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American Heart Journal

VOL. 48 SEPTEMBER, 1954 NO. 3

Original Communications

THE RELATIONSHIP OF ADRENALIN AND T-WAVE CHANGES IN THE ANXIETY STATE

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INTRODUCTION

DEPRESSION of the S-T segment and inversion of the T wave of the electrocardiogram are often transient and unassociated with basic alterations in cardiac muscle. Such changes have often been noted in response to stimuli producing anxiety, particularly in individuals who are emotionally unstable, but the mechanism of their production has not been clearly elucidated. It is the purpose of this paper to review briefly this problem and present the findings in a patient without evident myocardial disease in whom transient S-T segment depression and T-wave inversion were associated with anxiety-provoking stimuli and in whom these changes could be attributed to a "hypersensitivity" to endogenous Adrenalin.

Effect of Adrenalin—Many authors[1-4] have shown that small amounts of Adrenalin injected either subcutaneously or intramuscularly will depress the T wave. The magnitude of this depression is slight, ranging from 0.5 mm. to 1.5 mm., and is not significantly different among normal patients, those with angina pectoris, or those with the "irritable heart" syndrome. Levine and associates[4] have further demonstrated T-wave inversion in a normal patient but only when the Adrenalin was administered intravenously in a fairly large dose. The mechanism by which Adrenalin produces these changes is by no means clear. Raab[5] has presented evidence suggesting that Adrenalin induces an increased oxygen demand by the myocardium which is beyond that made available even by the increased muscular action and coronary dilatation evoked by the Adrenalin.

Effect of Anxiety.—Several investigators[6-8] have noted frequent T-wave depression and inversion in normal patients, during situations producing anxiety,

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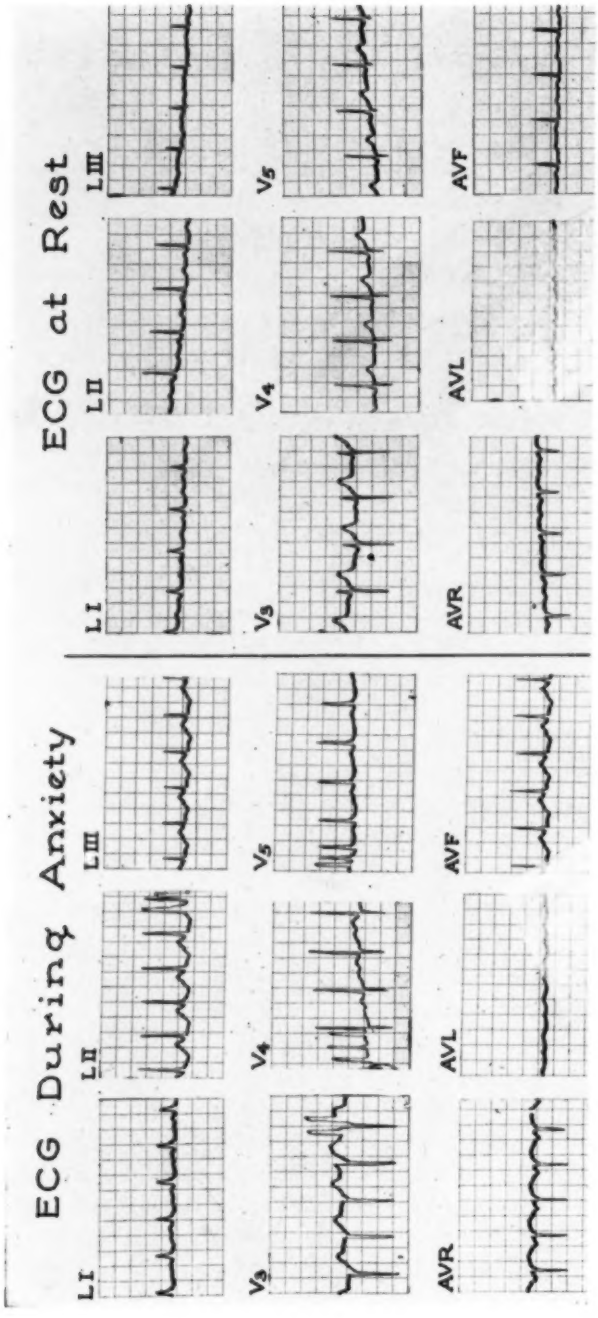

Fig. 1.—Electrocardiograms of patient J. E. during anxiety, and at rest after sedation and reassurance.

which would disappear rapidly with sedation and reassurance. Similar changes[9-12] have been described among patients with anxiety neuroses and psychotic states, occurring with a much greater frequency than in normal control series, and often disappearing following psychiatric treatment. Benedict,[13] on the other hand, studying the electrocardiograms of fifty normal medical students, just prior to their taking a major examination, found significant T-wave changes in only one subject. She therefore stated that the occurrence of electrocardiographic changes due to emotional stimuli is of rather infrequent occurrence depending on the strength of the stimulus and the susceptibility of the individual.

Stevenson and associates[14] studied thirty-five patients by taking continuous electrocardiographic tracings during discussions of stressful life situations. In six of these, they noted depression of the S-T segment and in eighteen, depression of the T wave of 0.5 mm. or more; in eight of these latter, T-wave inversion was observed. The same electrocardiographic changes could be produced by exercise, particularly during its initial phases, in certain of these patients. They concluded that sympathetic stimulation rather than cardiac anoxia was responsible for the T-wave changes and that this same mechanism may well be involved in the T-wave changes during emotional disturbance. Crede and co-workers[15] studied a patient in whom the production of anxiety evoked T-wave depression and inversion, which appeared and disappeared rapidly. They demonstrated that these changes were not due to alkalosis, anoxemia, or change in the position of the heart or diaphragm and in addition, elicited evidence suggesting that autonomic imbalance was not involved. They postulated that anxiety might be accompanied by an increase in circulating humoral agents which would directly affect myocardial electrical activity as well as produce tachycardia.

METHODS AND MATERIALS

The patient (J. E.) was a 21-year-old female, who was admitted to the hospital in an acute anxiety state mimicking a myocardial infarction. This syndrome was characterized by palpitation, precordial pain, shortness of breath, and weakness. Physical examination was normal, and the white blood cell count and the sedimentation rate were not elevated. The initial electrocardiogram showed S-T segment depression and T-wave inversion. It was subsequently noted that with sedation and reassurance the electrocardiogram reverted to normal (Fig. 1). Evaluation of her emotional state revealed evidence to support the diagnosis of a chronic anxiety neurosis with an acute exacerbation at the time of admission.

Continuous electrocardiographic tracings were taken in this patient while various situations were discussed and procedures carried out. In experiments involving the repeated administration of different amounts of Adrenalin or other solutions, an infusion was set up so that injections could be introduced into the tubing without the knowledge of the patient. In certain of the experiments, a face mask was employed through which ambient air, 100 per cent oxygen, or ambient air with 7 per cent carbon dioxide could be alternately introduced without the knowledge of the patient.

Two patients, a 26-year-old female (M. D.) and a 21-year-old male (L. T.), both convalescent from acute illnesses, with normal electrocardiograms and no evidence of emotional instability, were similarly studied. In addition, a fourth patient (A. L.), a 26-year-old male with considerable anxiety concerning his cardiac status along with symptoms and signs of multiple premature ventricular contractions, was also tested.

RESULTS

The results obtained in patient J. E. are presented in Fig. 2 which illustrates representative sections taken from continuous electrocardiographic tracings on Lead II. Similar changes occurred in all leads in which inversion had been present on admission (Fig. 1). The experiments were performed over the period of a week during which many of the procedures were repeated with identical results.

The discussion of possible heart disease, the threat of venipuncture, or actual venipuncture repeatedly caused S-T segment depression and flattening to inversion of the T waves (Fig. 2); however, with an infusion needle in place and following reassurance, the S-T segment would return to normal and the T wave would stabilize in an upright position. Accordingly, the changes described subsequently were always preceded by a control period during which the ECG revealed the pattern illustrated in Fig. 2, control.

Forcing the patient to hyperventilate, repeatedly produced S-T segment depression and T-wave inversion which appeared within 30 seconds at a time when the patient began to complain of the procedure, but before any true symptoms of hyperventilation appeared. When a breathing mask was placed on her face identical changes occurred immediately, but gradually disappeared as she became accustomed to the mask. Forcing her to hyperventilate through the mask with ambient air, or with 7 per cent CO_2 in ambient air, or 100 per cent O_2 all produced S-T segment and T-wave changes as previously described, which again appeared as the patient tired and began to complain of discomfort.

The injection of normal saline into the infusion tube, without the knowledge of the patient, caused no change in the ECG. Injection of 0.25 c.c. of a 1:10,000 solution of Adrenalin produced marked S-T depression and T-wave inversion simultaneously with the development of the same subjective symptoms (palpitation, precordial distress, shortness of breath, and weakness) that the patient experienced on admission. Following this, normal saline was injected, with the patient being told that it was Adrenalin. The same electrocardiographic abnormalities and subjective symptoms appeared as when Adrenalin itself was injected (Fig. 2).

Injection of 0.025 c.c. of 1:10,000 solution of Adrenalin, without her knowledge, produced S-T segment depression and T-wave inversion, although no subjective symptoms appeared. Injection of 0.025 c.c. of 1:10,000 solution of Adrenalin while the patient was breathing 100 per cent O_2 also caused the same electrocardiographic abnormalities. Furthermore, injection of a like amount of Adrenalin while the patient was breathing 100 per cent O_2 and following the administration of 1/100 grain of nitroglycerine still caused S-T depression and T-wave inversion (Fig. 2).

The rapidity of the development of these changes was quite striking. They appeared almost simultaneously with the patient's awareness of the stimulus or within several pulse beats thereafter but could not be accurately timed. When amounts of Adrenalin insufficient to produce subjective symptoms were injected, the time of appearance of changes approximated the circulation time.

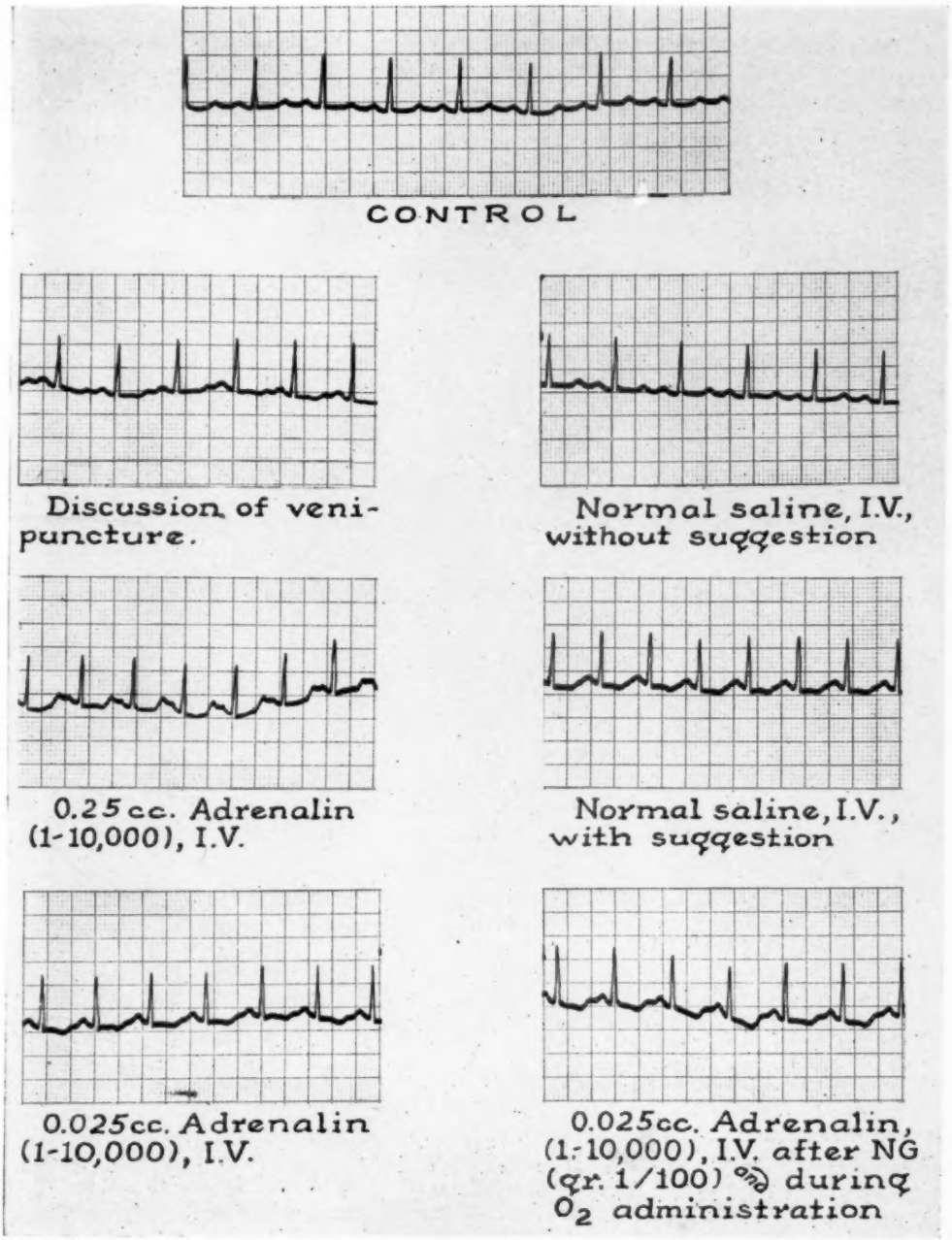

Fig. 2.—Sections from a continuous tracing on Lead II in patient J. E. illustrating the response to different procedures (see text for their description). A control period, identical to that shown, preceded each of the subsequent tracings.

The two emotionally stable patients and the patients with premature ventricular contractions and symptoms of cardiac anxiety with no organic heart disease, all of whom had normal electrocardiograms, revealed no significant changes with similar maneuvers. The threat of venipuncture, actual venipuncture, and discussion of anxiety-producing life situations were without effect.

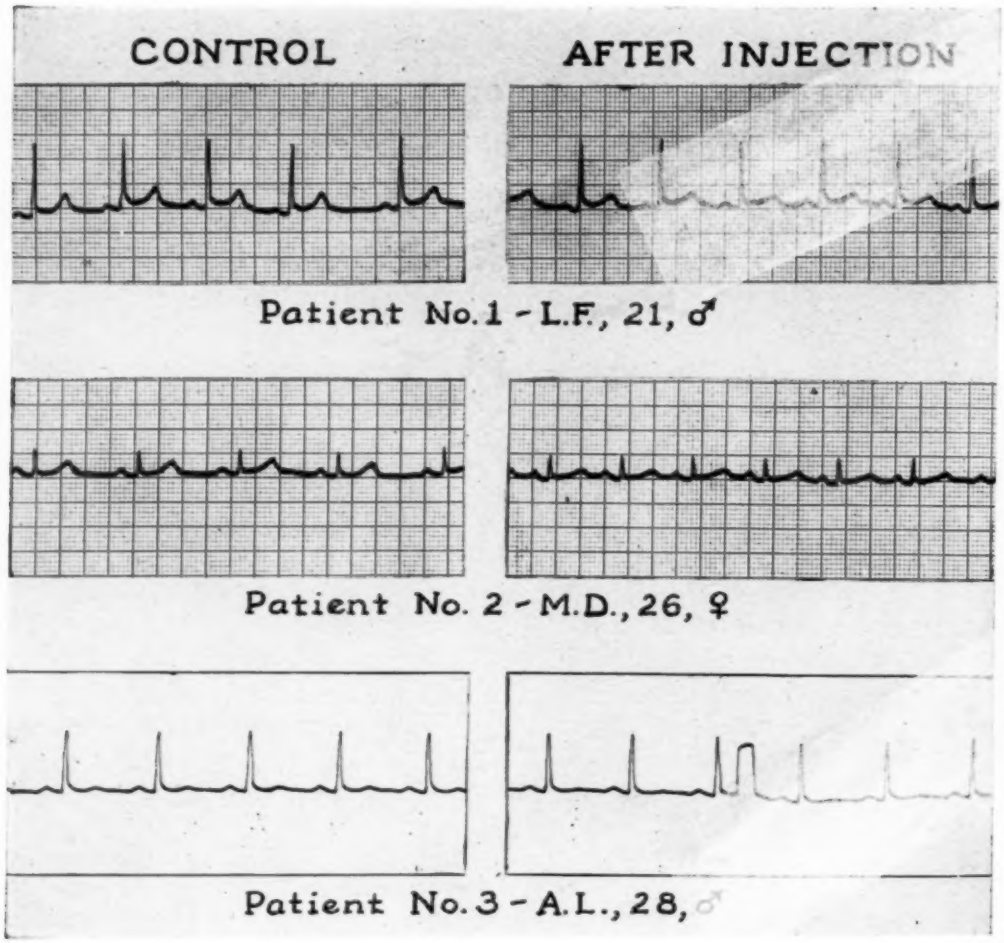

Fig. 3.—Sections from continuous tracings on Lead II in normal patients illustrating response to 0.025 c.c. of Adrenalin (1:10,000) intravenously.

Injection of 0.025 c.c. to 0.5 c.c. of the 1:10,000 solution of Adrenalin caused only slight flattening of the T wave with no inversion, although doses above 0.1 c.c. usually produced subjective symptoms. Fig. 3 illustrates the results obtained in these three patients with the 0.025 c.c. dose.

DISCUSSION

This series of experiments clearly demonstrated that in patient J. E., situations producing anxiety resulted in S-T depression and T-wave inversion and that these changes could be reproduced by the injection of Adrenalin even in

quantities too small to be subjectively appreciated. It therefore seems likely that the electrocardiographic abnormalities which she demonstrated during anxiety were caused by endogenous Adrenalin. Furthermore, since similar small amounts of exogenous Adrenalin did not produce significant changes in two normal patients or even in one patient with an intermittent cardiac arrhythmia, it may be concluded that the myocardium of patient J. E. displayed "hypersensitivity" to the action of Adrenalin.

The data also demonstrate that the effect of Adrenalin on the S-T segment and T waves in patient J. E. could not be prevented by the breathing of 100 per cent 0_2 and/or the administration of nitroglycerine. Effects of Adrenalin on the electrocardiogram were therefore not mediated by myocardial anoxia resulting from diminished coronary artery flow. It is more likely that Adrenalin had a direct effect on the electrical activity of the myocardial muscle.

Similarly, although T-wave changes appeared with forced hyperventilation, their appearance when hyperventilation was performed in the presence of high concentrations of CO_2 confirms previous evidence[15] that hypocapnia and respiratory alkalosis are not the cause of this phenomenon. It is more likely that forced hyperventilation in itself was a stressful procedure for her, resulting in the endogenous release of Adrenalin.

It is tempting to speculate from these data that individuals with an anxiety state possess a "hypersensitivity" to endogenous Adrenalin, at least as it affects the myocardium, which might account for the frequent demonstration of S-T segment and T-wave changes in emotionally unstable patients. The possibility cannot be eliminated, however, that the sensitivity is unrelated per se to anxiety but is merely more readily apparent in the anxious individual who is more apt to provoke an endogenous secretion of Adrenalin. Nor can it be said that the anxiety state is necessarily always accompanied by myocardial sensitivity to Adrenalin, even in instances where cardiac symptoms are present, or that it is necessary for the existence of functional cardiac symptomatology. It need only be pointed out in this regard that many individuals with "cardiac neuroses" have normal electrocardiograms and that patient A. L. who had both cardiac symptoms as well as considerable cardiac anxiety showed no changes like those of patient J. E.

It would seem most reasonable, therefore, to assume that in certain individuals the myocardium is particularly sensitive to the effect of Adrenalin and that these effects can be evoked by anxiety-producing stimuli. The mechanism by which Adrenalin produces these changes is probably not related to blood flow through the coronary arteries but seems more likely due to a direct effect of Adrenalin on the myocardium. These considerations suggest an explanation for T-wave changes in the anxiety state which offer an alternative hypothesis to the concept of autonomic imbalance which has been invoked in the past.

SUMMARY

The mechanism of T-wave inversion in an emotionally unstable patient was studied by means of continuous electrocardiographic tracings. It was demon-

strated that these changes resulted from (1) the probable endogenous production of small amounts of Adrenalin during anxiety; (2) hypersensitivity of the myocardium to Adrenalin.

The authors wish to express their appreciation to Dr. William F. Miller and Mr. Robert Cade for their assistance in the ventilatory studies.

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ELEVATION OF THE RS-T SEGMENT, APPARENT OR REAL, IN THE RIGHT PRECORDIAL LEADS AS A PROBABLE NORMAL VARIANT

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THE significance of deviation of the RS-T segment in the electrocardiogram of patients suspected of having acute lesions of the myocardium is well known and needs no discussion here. Although there are no rigid standards for deviation of the RS-T segment, and the allowable upward deviation for precordial leads is in general greater than that for limb leads, a deviation of more than 2 mm. upward or downward is commonly looked upon with suspicion. However, deviation even below the normal limits may be observed in acute myocardial infarctions and yet be considered significant, especially if the shape of the RS-T segment is altered.

However, over a period of years, we have repeatedly observed tracings in which the RS-T segment appeared to be abnormally elevated in certain precordial leads of individuals in whom, we believe, no cardiac disease was present. In several instances, the pattern has persisted without change for as long as five years, thus eliminating the possibility of acute myocardial damage. From this experience, ten cases have been selected, because the degree of the apparent segment deviation and abnormality of configuration were particularly apparent and because, after careful study, no collateral evidences of heart disease were discovered (Table I).

In these tracings, the apparent RS-T segment was observed to be elevated in one or more of the right precordial leads, but the left precordial leads were normal (Figs. 1 and 2). Characteristically, the apparent RS-T segment arises from an R′ wave, is most elevated at its origin, and then slopes gradually downward resembling the latter half of a T wave.

A comparison of V, CR, and CF leads shows that the described pattern was present and similar in all comparable positions of the precordial electrode (Figs. 1 and 2). No suggestion of abnormality of the limb leads was found in the standard and unipolar limb leads of six of these subjects and these leads were well within the normal range of variation in the others; in four there was a slight elevation of the RS-T segment in Lead aV_L and in one of these a slight depression of the RS-T segment in Lead aV_R.

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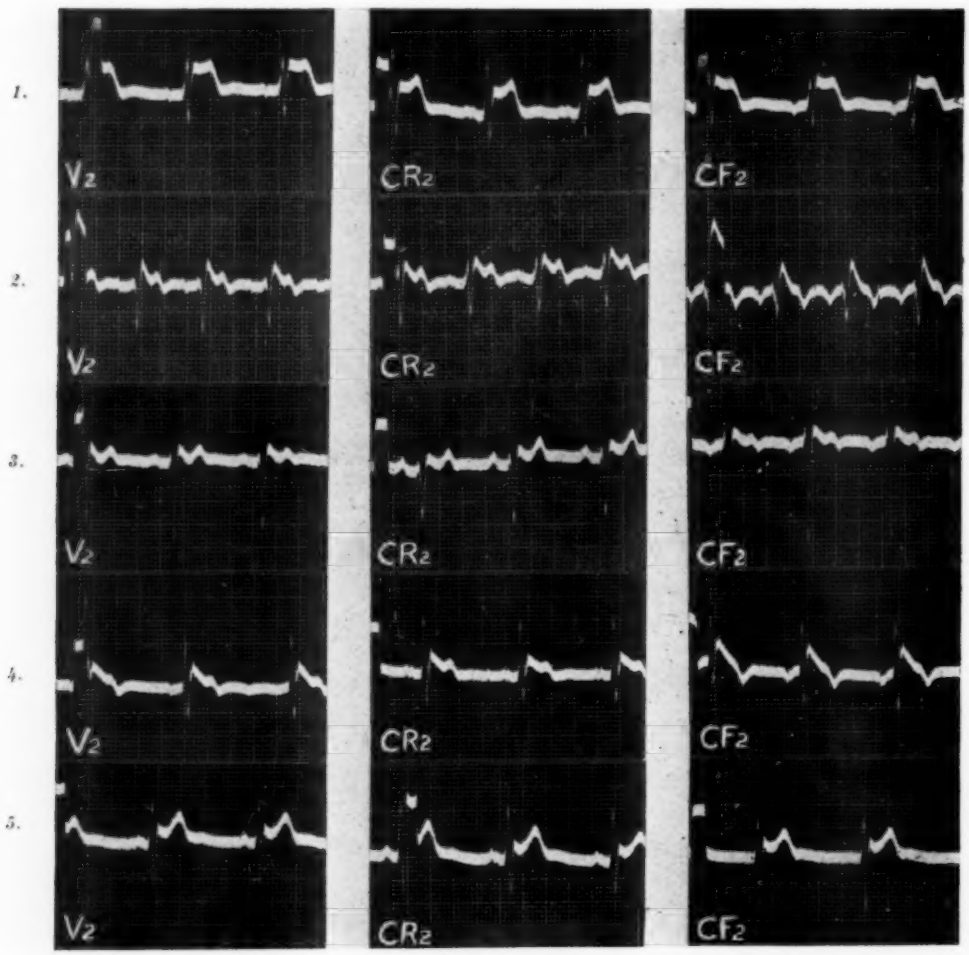
Thus, we are considering a pattern which might be considered abnormal only in the right precordial leads; it is unlike that described by Goldman[1] in the mid- and left-precordial leads. It is evident from standardization square-waves of Figs. 1 and 2 that this pattern is not a technical artifact caused by overshooting of the recording instrument. Similar standardization patterns were recorded in all of the other leads illustrated.



Figs. 1 and 2.—Single precordial leads of ten patients showing marked positive RS-T segment deviation. Comparison of V, CR, and CF leads: all were made in the fourth intercostal space to the left of the sternum.

The pattern described above was present in hearts in the transverse and vertical electrical positions. Change from the recumbent to the sitting position caused no significant change in the configuration of the pattern described above (Fig. 3). However, change in position of the exploring electrode to a higher or

lower intercostal space, as would be expected, showed some change in the appearance of the QRS complexes and T waves, but in each case studied the configuration of the apparent RS-T segment remained abnormal according to usual standards (Fig. 4).

The presence of this pattern suggested injury to the myocardium, but this opinion was considered untenable because (1) in all cases on re-examination,

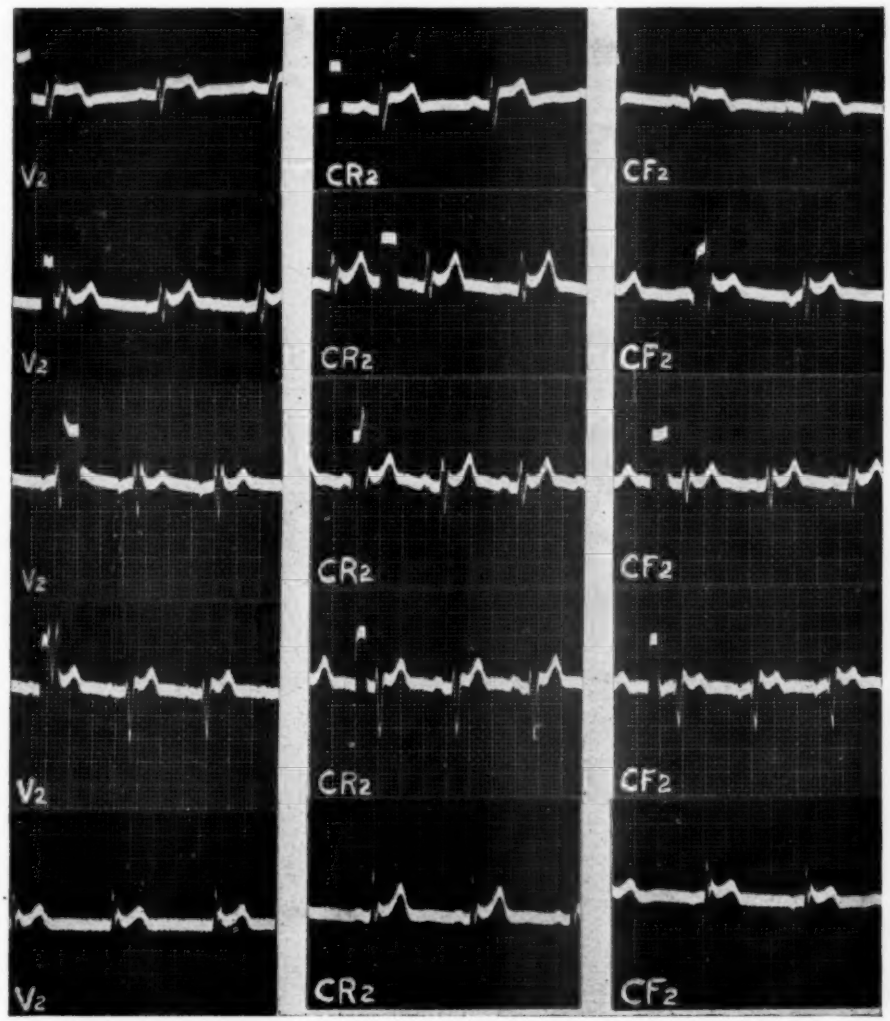


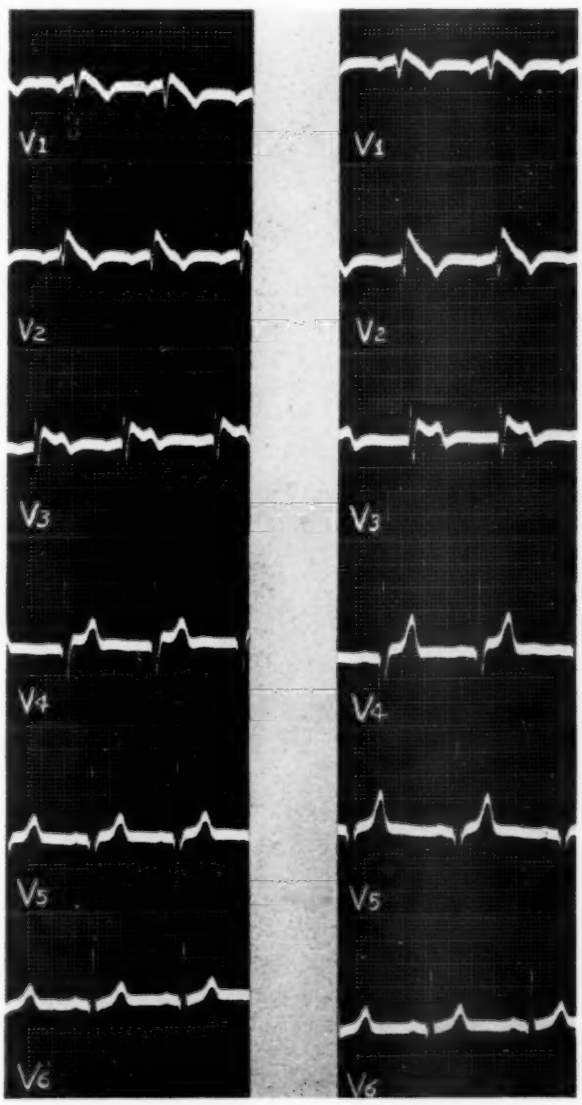
Fig. 2.—(*For legend see opposite page.*)

the RS-T segment persisted longer than usual in cases with proved acute injury of the heart. In four cases the pattern persisted longer than five years. (2) No evidence was found to indicate a previous myocardial infarction and subsequent ventricular aneurysm, pericarditis, and endocrine or metabolic disorder.

TABLE I

CASE	AGE	SEX	CHIEF COMPLAINT	BLOOD PRESSURE	HEART SIZE	AORTA	CLINICAL DIAGNOSIS	DURATION OF OBSERVATION
1	61	M	Substernal pain	150/90	Normal	Slightly dilated	Esophageal spasm	5 yr., 9 mo.
2	49	M	None, abnormal electrocardiogram found by family physician on routine examination	140/90	Normal	Normal	Peptic ulcer	6 yr.
3	57	M	None	135/80	Normal	Normal	No definite evidence of heart disease	5 yr.
4	46	M	Upper abdominal pain, unrelated to effort	110/70	Normal	Normal	Spastic colitis	3 yr. 5 mo.
5	48	M	Pain in the upper sternal region on excitement	110/70	Top normal	Normal	Esophageal spasm	11 mo.
6	61	M	None, routine examination	150/90	Normal	Slightly elongated	No definite evidence of heart disease	5 yr., 8 mo.
7	34	M	Easy fatigue, sighing respiration	130/80	Normal	Normal	Neurocirculatory asthenia	8 mo.
8	45	M	Momentary pain over the precordium, unrelated to effort, marked sighing	130/80	Normal	Normal	Neurocirculatory asthenia	14 mo.
9	50	M	None, abnormal electrocardiogram found by family physician on routine examination	146/80	Normal	Normal	No definite evidence of heart disease	10 mo.
10	67	M	Severe headache	144/90	Normal	Normal	Possible cerebral neoplasm	11 wk.

(3) Eight of the cases had no symptoms in any way suggestive of cardiac disease; two had symptoms somewhat suggestive of angina pectoris, but subsequent examinations disclosed other bases for their symptoms and no supporting evidence of heart disease.



A. *B.*

Fig. 3.—Patient No. 2, six years after the original electrocardiogram, showing but slight change in the configuration of the precordial leads with change in position. *A*, Sitting. *B*, Recumbent.

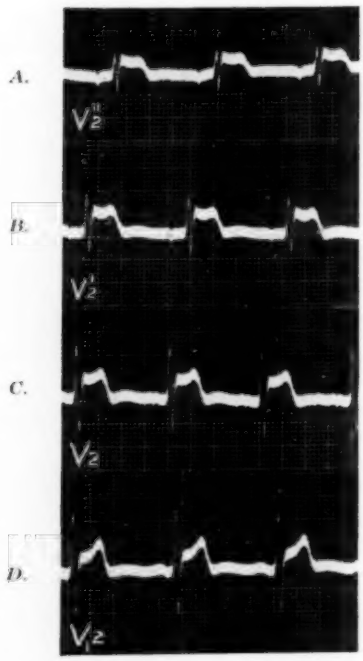


Fig. 4.—Patient No. 1, five years and nine months after the original electrocardiogram showing a change in the configuration with change in the position of the exploring electrode. *A*, Second intercostal space to the left of the sternum. *B*, Third intercostal space. *C*, Fourth intercostal space. *D*, Fifth intercostal space.

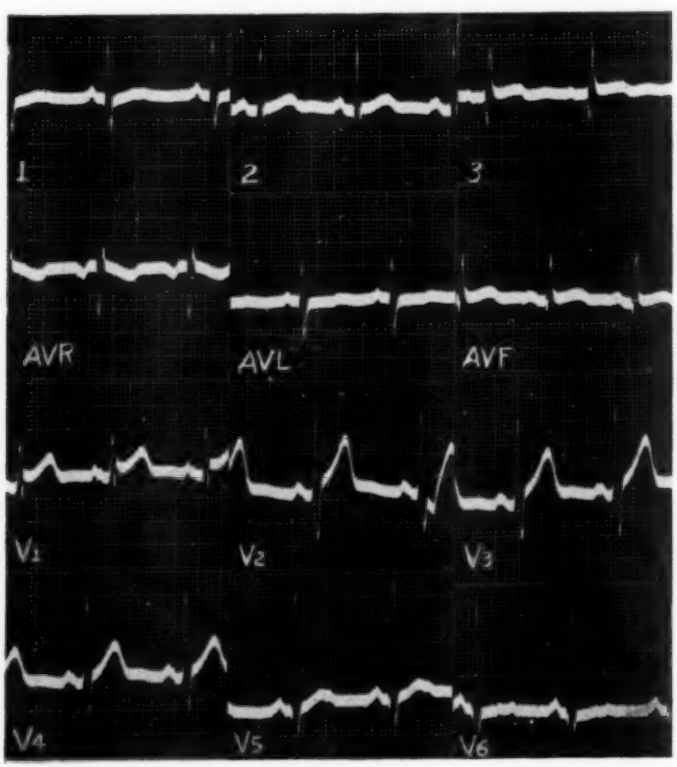


Fig. 5.—Electrocardiogram of a man, aged 30, made the day following an attack of severe substernal pain. Elevation of the RS-T segment in the right precordial leads is seen with only slight T-wave changes in the limb leads.

Occasionally, this pattern may be the cause of confusion in localizing areas of myocardial injury or infarction and, unless previous electrocardiograms are available, may be considered evidence of acute injury to the anteroseptal surfaee of the left ventricle. Fig. 5 is the electrocardiogram of a man, age 30, made thc day following an attack of severe substernal pain and Fig. 6 is the tracing made fourteen months later. Apparently, the deviation of the RS-T segment in the

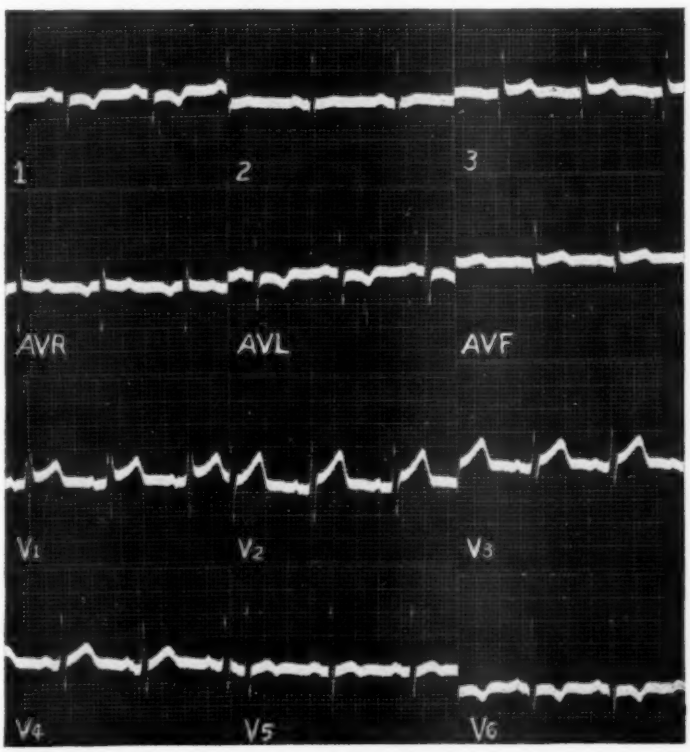


Fig. 6.—Tracing of same patient as Fig. 5 made fourteen months later; the deviation of the RS-T segment in the right precordial leads persists, whereas the T waves have become abnormal in Leads I, aV_R, and aV_L.

right precordial leads shows a normal variant persisting, while electrocardiographic abnormalities, associated with myocardial disease, are developing elsewhere. Another demonstration of a normal variant with superimposed electrocardiographic abnormalities is shown in Fig. 7, the tracing of a man, age 68, who suffered a posterior myocardial infarction on Sept. 11, 1952. The appearance of positive deviation of the RS-T segment was the cause of concern until a tracing (Fig. 8), made May 29, 1950, was made available for comparison and showed a similar deviation in the right precordial lead.

In describing this pattern, the term "apparent RS-T segment elevation" has been used. It is probable that in some of these tracings, (notably Case 8) what might be considered an RS-T segment is, in actuality, a portion of the QRS

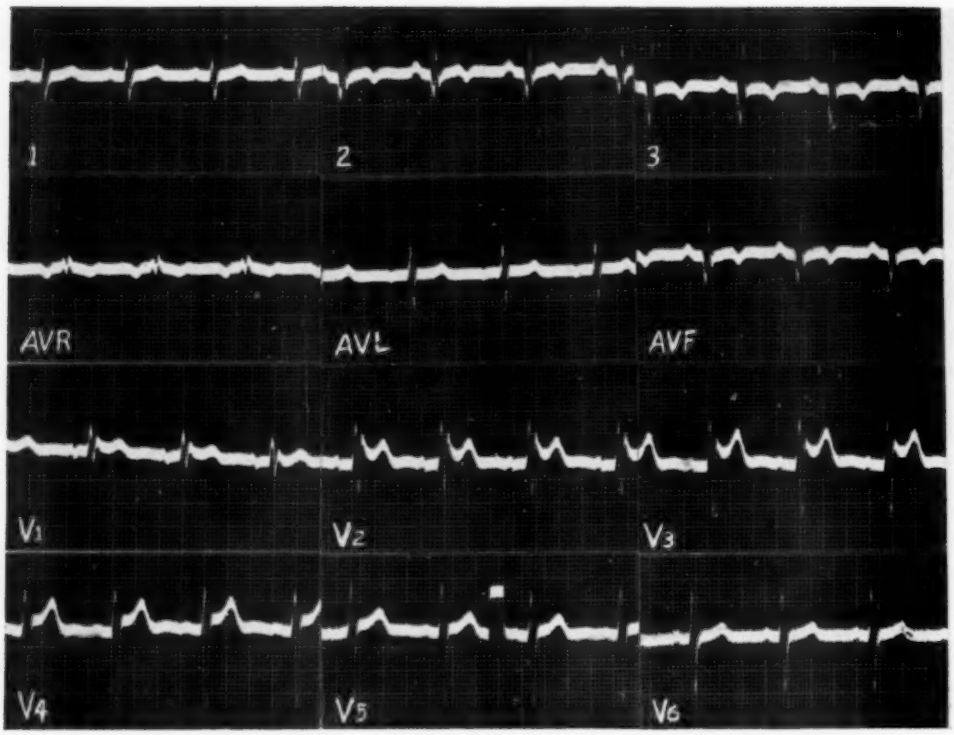


Fig. 7.—Tracing of a man, aged 68, who suffered a posterior myocardial infarction on Sept. 11, 1952. The infarction pattern is typical except for the RS-T segment elevation in the right precordial leads.

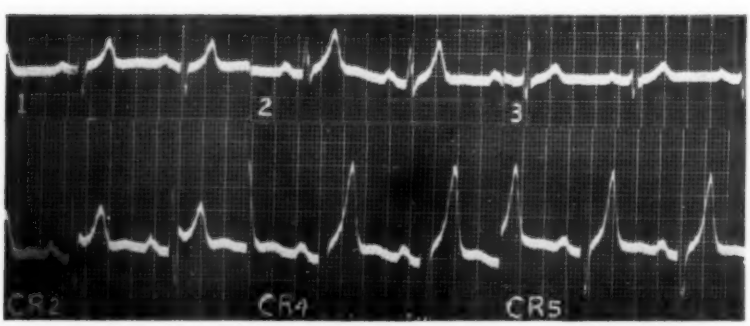


Fig. 8.—Electrocardiogram of same patient as Fig. 7 made May 29, 1950, showing abnormal configuration of the RS-T segment in the right precordial leads.

complex associated with a localized intraventricular conduction defect, such as that described by Osher and Wolff.[2] However, in other instances (notably Cases 1 and 6), the appearance cannot be explained on the basis of QRS prolongation. Whatever the physiologic explanation for the phenomenon may be, a pattern of this type arouses suspicion of myocardial disease or injury. Nevertheless, it must be emphasized that this pattern may be considered as a possible normal variant only if careful study, including unchanging serial electrocardiograms, reveals no corroborative evidence of heart disease.

CONCLUSIONS

Ten examples of apparent high elevation of the RS-T segment in the right precordial leads, without other evidences of heart disease, are presented. The available evidence strongly suggests that this finding is not necessarily indicative of myocardial disease but may represent a normal variant.

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THE VECTOR AND ALGEBRAIC RELATIONSHIP OF THE CF AND V CHEST LEADS

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CONSIDERABLE confusion exists concerning the relative merits of the CF and V precordial leads. Some have expressed the opinion that one set is "better" than the other.[1] The pamphlet entitled "Examination of the Heart", published in 1951 by the American Heart Association, contains the statement ". . . CF precordial leads are more sensitive but less specific than V leads."

The theoretical advantages of an indifferent electrode which approximates a zero potential would appear, on the surface, to make the V leads a truer representation of the underlying electrical phenomena. One can hardly deny, however, the ample evidence presented in which the CF leads have shown, in pathologic hearts, more consistent T-wave inversion than the V precordial leads.[2] It is the purpose of this paper to analyze this apparent contradiction.

Cohen and Glicksman[3] have described the relationship between the bipolar and unipolar leads and have pointed out that there is no basic difference in the information obtained by both methods. Graettinger and associates,[4] using the hexaxial reference scheme suggested by Sodi-Pallares, have shown how the unipolar and bipolar leads complement one another. Data will be presented to show that there is an intimate algebraic and vector relationship between the CF and V leads which makes it possible to determine the CF pattern if the V and V_F (or aV_F, which equals 3/2 V_F) leads are available. In similar fashion the CR pattern can be determined if the V and V_R leads are available. If one represents Leads V, CF and VF as the sides of a triangle (Fig. 1), it is clear that CF equals V minus VF in the same fashion that I equals II minus III in the classical Einthoven equation. By like reasoning CR equals V minus VR when a triangle is constructed from vectors that represent these leads.

The equations presented indicate that a large T wave in the leg electrode (V_F or aV_F) may account for negativity in the CF lead while the corresponding V lead shows positivity. With this relationship in mind the electrocardiograms of six patients are analyzed. In four the spatial disposition of the QRS and T vectors is studied by the method of Grant and Estes[5] in order to determine whether widening of the QRS-T angle, which is correlated with the ventricular gradient, would in certain instances produce sufficient footward deviation of the

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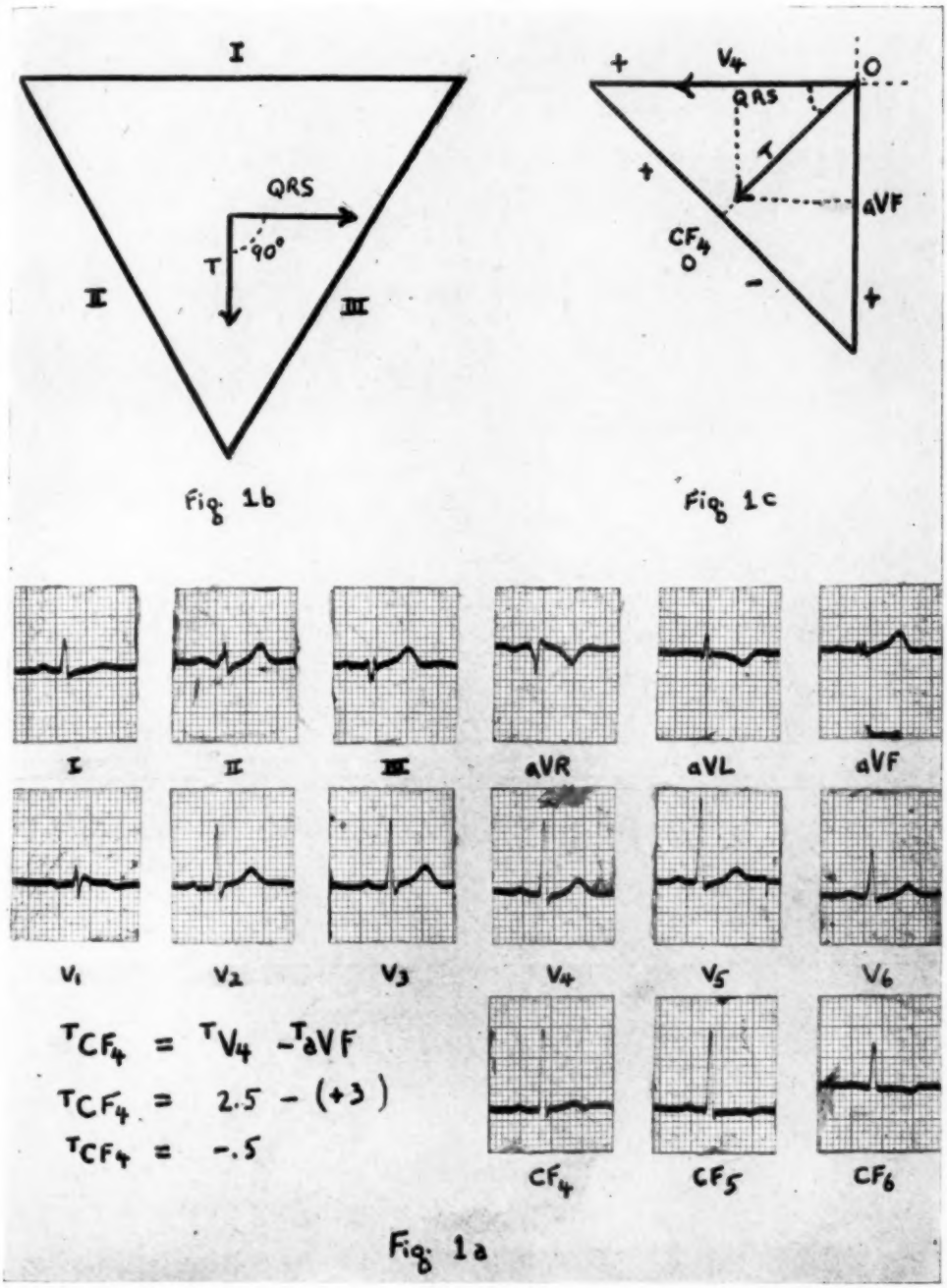

Fig. 1.—*a*, Electrocardiogram of Case 1 showing T-wave abnormalities in the left precordial CF leads and normal V leads; *b*, QRS-T angle of 90° in the frontal plane in Case 1. *c*, QRS and T vectors in a plane defined by the chest electrode at V_4, the left leg electrode and the null point.

T vector to result in large T potentials at the left leg electrode. In two cases electrocardiograms are presented which show the usual disposition in space of the QRS and T vectors in a normal and a pathologic heart. In these, footward direction of the T potentials is not conspicuous and the T waves in the CF and V precordial leads are similar.

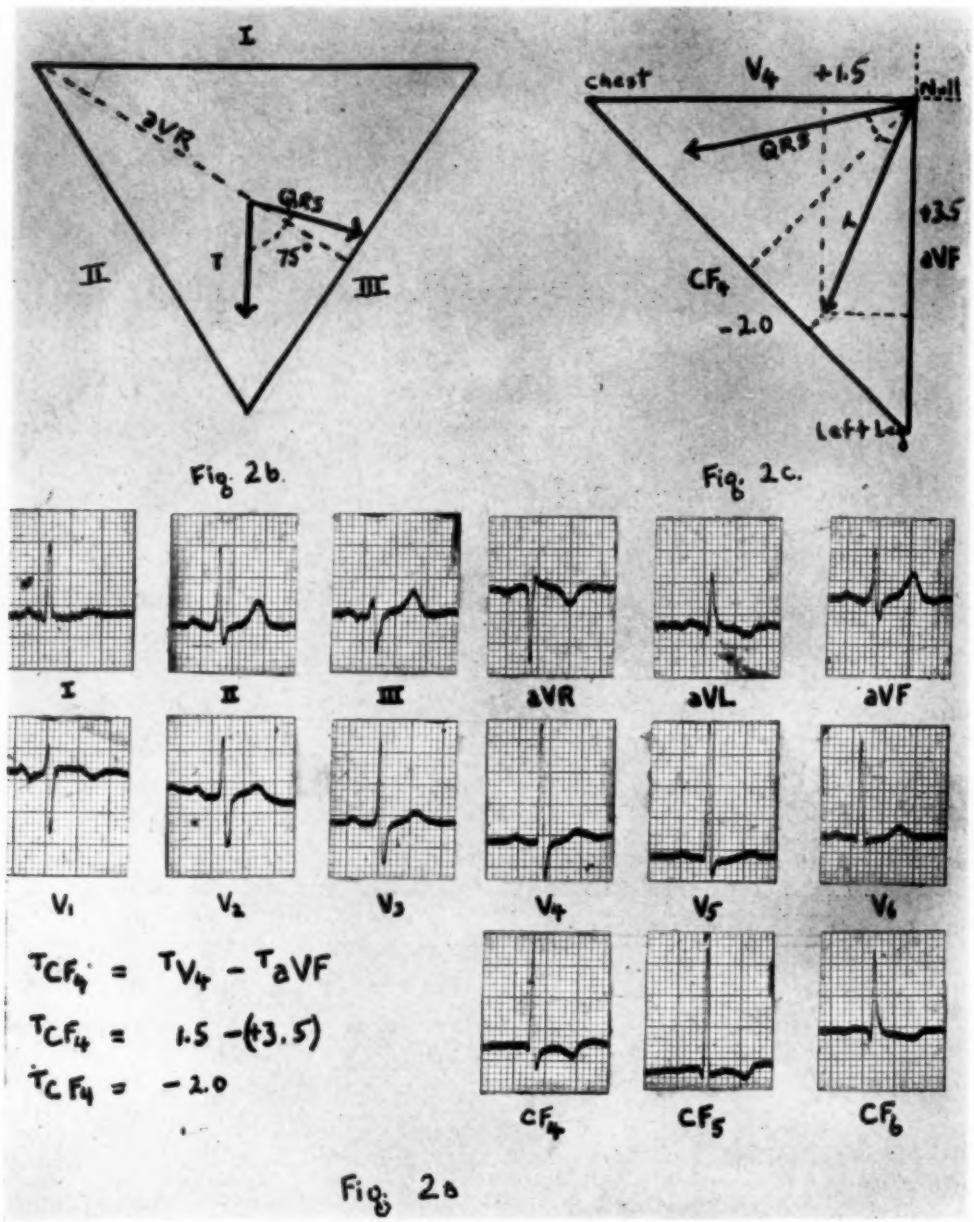

Fig. 2.—*a*, Electrocardiogram of Case 2 showing decidedly abnormal T waves in the CF leads. *b*, Vector representation in the frontal plane showing the footward deviation of the T vector. *c*, T vector in the sagittal plane showing its projection onto the negative side of CF_4.

CASE REPORTS

CASE 1.—Fig. 1, *a* demonstrates the electrocardiogram of a 59-year-old male, who developed severe interscapular pain with radiation to both forearms on exertion or exposure to cold weather. The patient was obese and squat. This is an example of a horizontal, counterclockwise rotated heart with an abnormally wide QRS-T angle in the frontal plane (Fig. 1,*b*). QRS in aV_F is equiphasic and the QRS vector is, therefore, perpendicular to aV_F and parallel to Lead I. The T wave is smallest in Lead I and tallest in aV_F, hence parallel to aV_F. By construction, the QRS-T angle is 90° and, therefore, abnormal in the frontal plane.[6] The pathologic significance of T_3 taller than T_1 in a horizontal heart, as pointed out by Dressler and Roesler,[7] is really an empirical method of evaluating the width of the QRS-T angle in the frontal plane. In this tracing T_{aVF} is 0.5 mm. taller than T_{V4}. Hence T_{CF4} is slightly inverted since the potential at CF_4 is equal to the difference in potential between V_4 and V_F, and all T_{CF} potentials to the left of CF_4 will be negative although all T waves in the V leads are positive.

The tracing illustrated is an example of a pathologic electrocardiogram in which the CF leads show a left strain or coronary insufficiency pattern but in which the V leads would be regarded as normal. This does not imply that the V leads were inaccurate. It indicates, rather, that the footward deviation of the T vector has produced T waves which are taller in aV_F than in the V leads over the left side of the precordium. The upright T waves in the V leads and the inverted T waves in the CF leads tell us that the T vector is directed downward.

The fundamental relationship of the T vector (as well as all cardiac vectors) to the CF and V precordial leads is shown in Fig. 1,*c*. Leads aV_F, V_4 and CF_4 are represented diagrammatically in a plane defined by the left leg electrode, the chest electrode at V_4, and the theoretical null point. For brevity's sake this will be referred to as a sagittal plane although it is not the true sagittal plane since it cannot be assumed that the null point lies directly behind the exploring chest electrode. The triangle thus formed is assumed, very roughly, to be a right angle triangle. The inaccuracies implied in the diagram are recognized but the figure serves to illustrate a useful relationship. The T vector, which is perpendicular to the hypotenuse of the triangle representing CF_4, will be equally projected on V_4 and aV_F. Hence, T_{CF4} will be close to zero and, in this instance, it will be recorded as a flat or slightly inverted wave. T_{V4} and T_{aVF} are upright and about equal in magnitude.

CASE 2.—Fig. 2,*a* is another example of a patient with known coronary artery disease whose QRS-T angle is roughly 75° in the frontal plane (Fig. 2,*b*). The electrical axis of QRS is again leftward and the transitional QRS pattern is at V_2. There is a tall T_{aVF} with even more conspicuous T-wave inversion in the CF leads than in the previous case, although the T waves in the V precordial leads are upright and within normal limits. The spatial relationship of the T potentials is graphically illustrated in Fig. 2,*c*, in which the T vector is seen to lie well to the footward or negative side of the mid-point of the line representing CF_4, causing T_{CF4} to be negative. A large positive T potential is subtended on aV_F and a smaller positive T potential on V_4. The QRS vector on the other hand lies on the chestward or positive side of the mid-point of the hypotenuse representing Lead CF_4, causing the QRS to be positive in CF_4, V_4 and aV_F. This is a diagrammatic representation of the fundamental algebraic relationship T_{CF4} equals TV_4 minus T_{aVF}. In this instance T_{CF4} equals 1.5 minus 3.5 or that is, −2.0 mm. One need not have recorded the CF leads to demonstrate that the T waves would be negative. It could have been predicted from the fact that T_{aVF} is taller than any of the T waves in the V precordial leads.

CASE 3.—This illustrates the electrocardiogram of an individual who clinically had a myocardial infarct. This is a frankly pathologic electrocardiogram which shows anteroseptal infarction as contrasted with the two previous cases described which illustrated the "left strain pattern."

Fig. 3,*a* is the tracing contrasting the V leads, in which the abnormalities consist of a QS deflection in V_2 and a low T_{V_4}, and the CF leads which are somewhat more typical of anteroseptal infarction in that the T waves show more characteristic changes. The upright T waves in the V leads are again due to the fact that the T vector in this semivertical heart (Figs. 3,*b* and *c*) is directed toward the left leg producing a positive deflection of 2.5 mm. in aV_F, while subtending a smaller positive deflection of only 1.0 mm. on V_4. The difference between the two produces a negative T wave

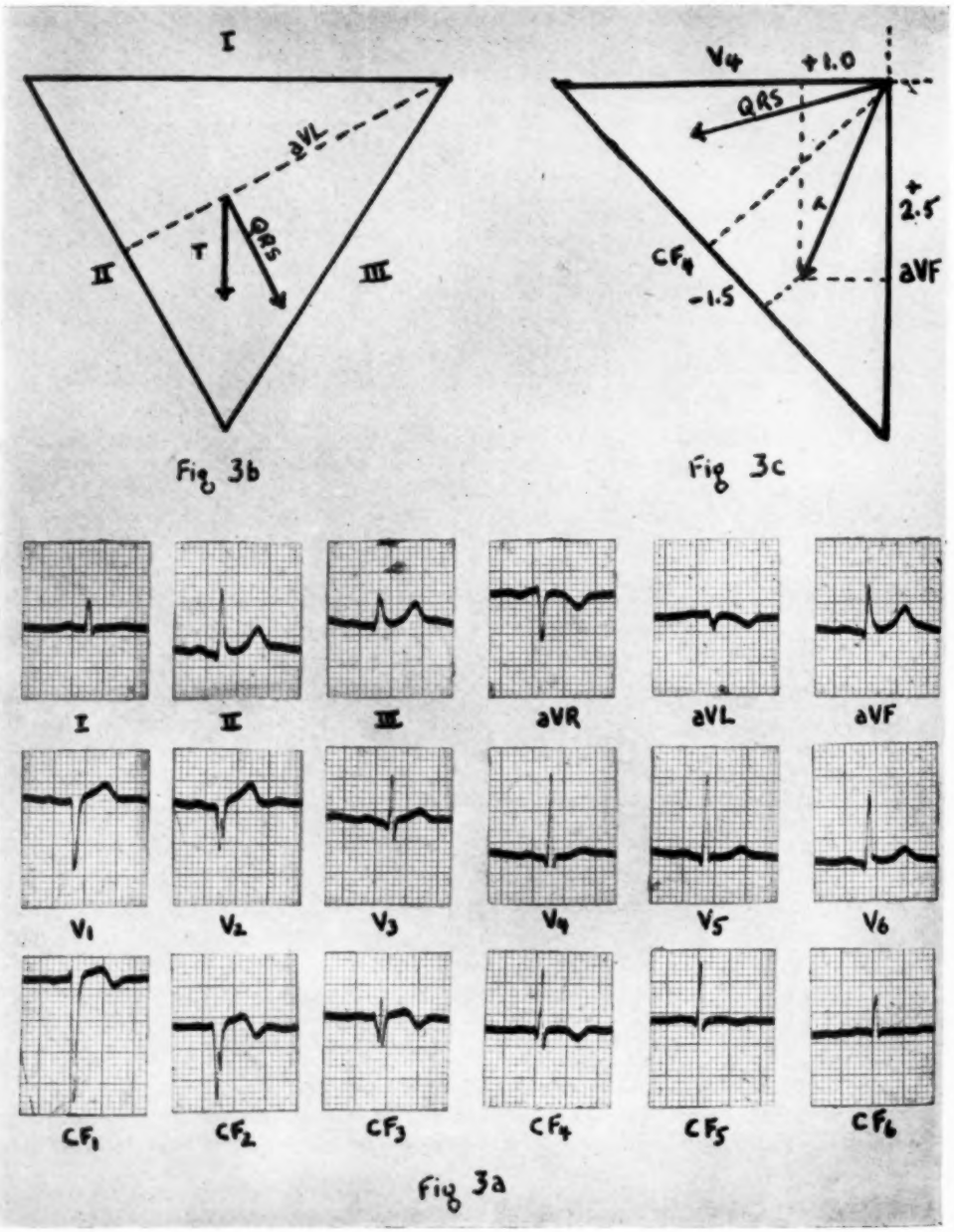

Fig. 3.—*a*, Electrocardiogram of Case 3 showing evidence of anteroseptal infarction with more characteristic changes in the CF leads. *b*, QRS-T angle in the frontal plane. *c*, A sagittal representation of the T vector showing its footward deviation.

in CF_4 and similarly in the other CF leads. An interesting sidelight is the appearance of a deeper, wider Q wave in CF_3 than in V_3. This is due to the same algebraic relationship but is more difficult to demonstrate, since it would require simultaneously recorded tracings at rapid camera speeds for the addition and subtraction of potentials at identical, brief instants during the recording of QRS.

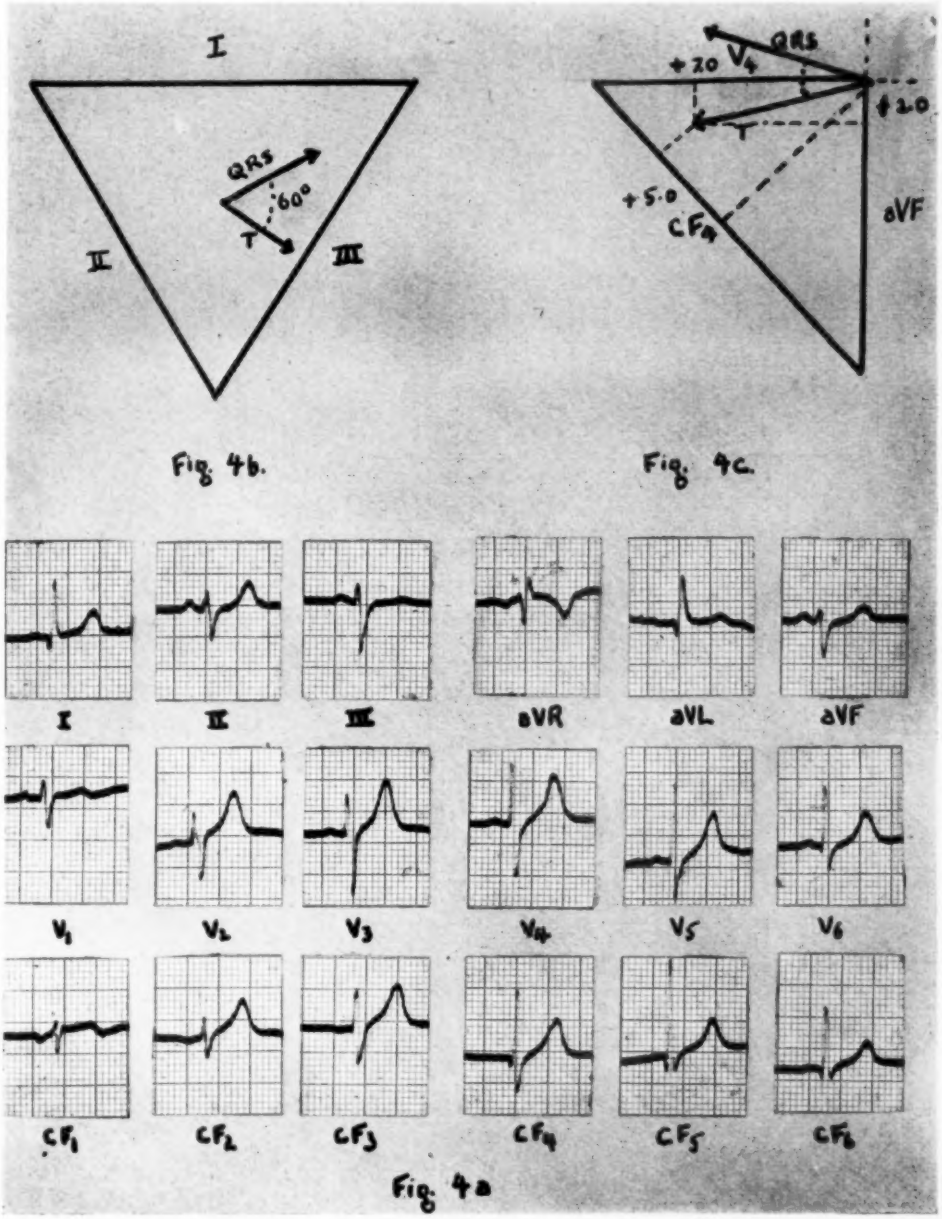

Fig. 4.—*a*, Electrocardiogram of Case 4, a normal, horizontal heart. *b*, Frontal plane disposition of the QRS and T vectors. *c*, Sagittal representation of the QRS and T vectors, showing a narrow angle between them.

CASE 4.—Here is presented a demonstration of the T vector relationship to the CF and V precordial leads in a normal horizontal heart in which the CF and V leads resemble one another. The patient was a 50-year-old, short, squat man who gave no history or findings suggestive of heart disease and whose heart was normal in size and shape although transversely placed. The electrocardiogram (Fig. 4,*a*) is normal. The QRS is equiphasic in Lead II and tallest in aV_L and

Lead I suggesting that the QRS vector is pointing approximately at the left arm. The flattest T wave is in Lead III indicating that the T vector in the frontal plane is perpendicular to that lead. By construction (Fig. 4,*b*) the QRS-T angle is 60° which is probably close to the upper limit of normal. In the sagittal plane (Fig. 4,*c*) as defined by the triangle formed by the chest electrode at V_4 and the left leg electrode and the null point, the T vector is seen to point well anteriorly.

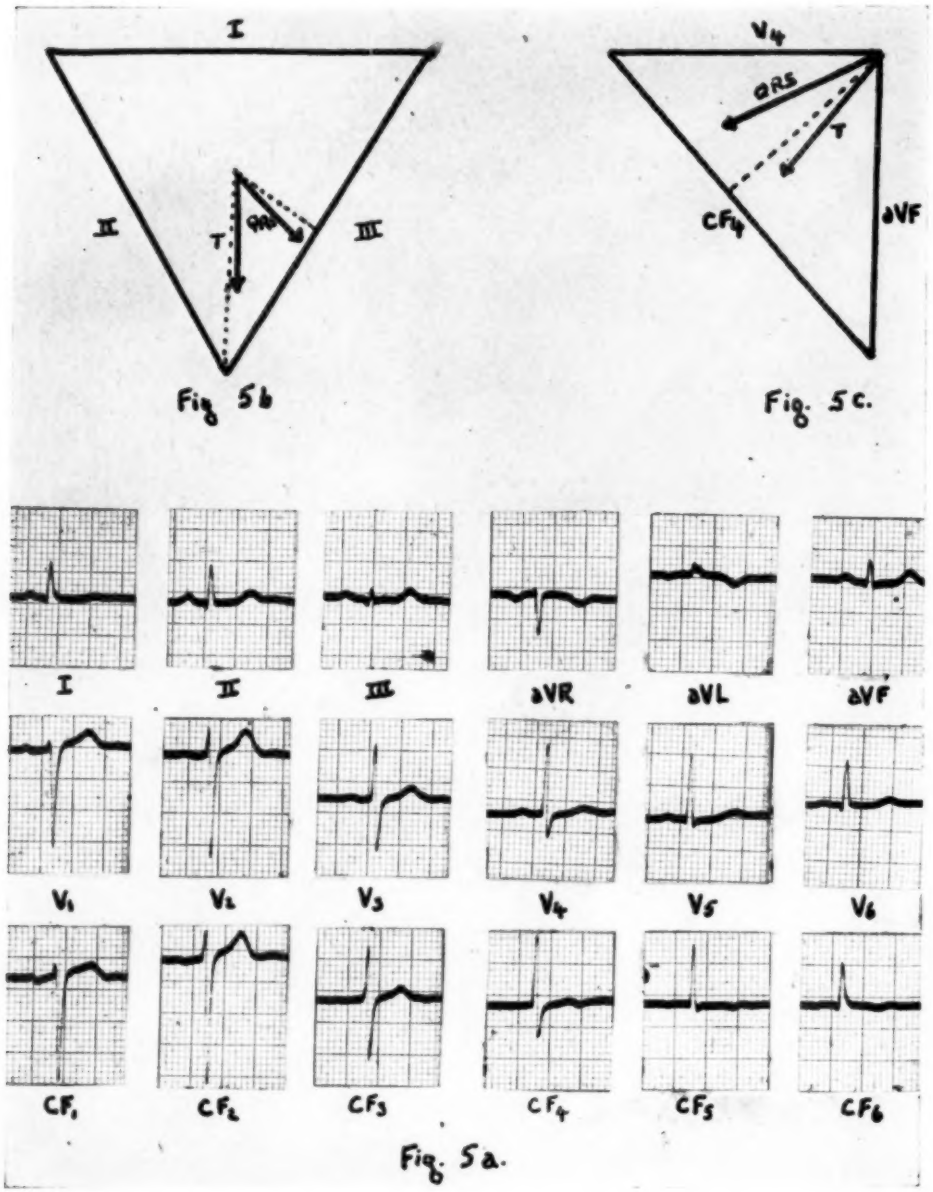

Fig. 5.—*a*, Electrocardiogram of Case 5 in which there was no history or findings suggestive of organic heart disease. *b*, Frontal plane projection showing a comparatively narrow QRS-T angle. *c*, Sagittal representation of vectors demonstrating a narrow angle and footward deviation of the T vector to the negative side of CF_4.

The QRS-T angle in the sagittal plane is narrow. T_{aVF} is 2.0 mm. in height, T_{V_4} is 7.0 mm. tall and T_{CF_4}, which is the difference, is 5.0 mm. tall. The T waves though somewhat lower than those in the V leads are essentially similar. As long as the T waves in the V leads are taller than T_{aVF} we derive no additional information from the CF leads with respect to the form of the T waves.

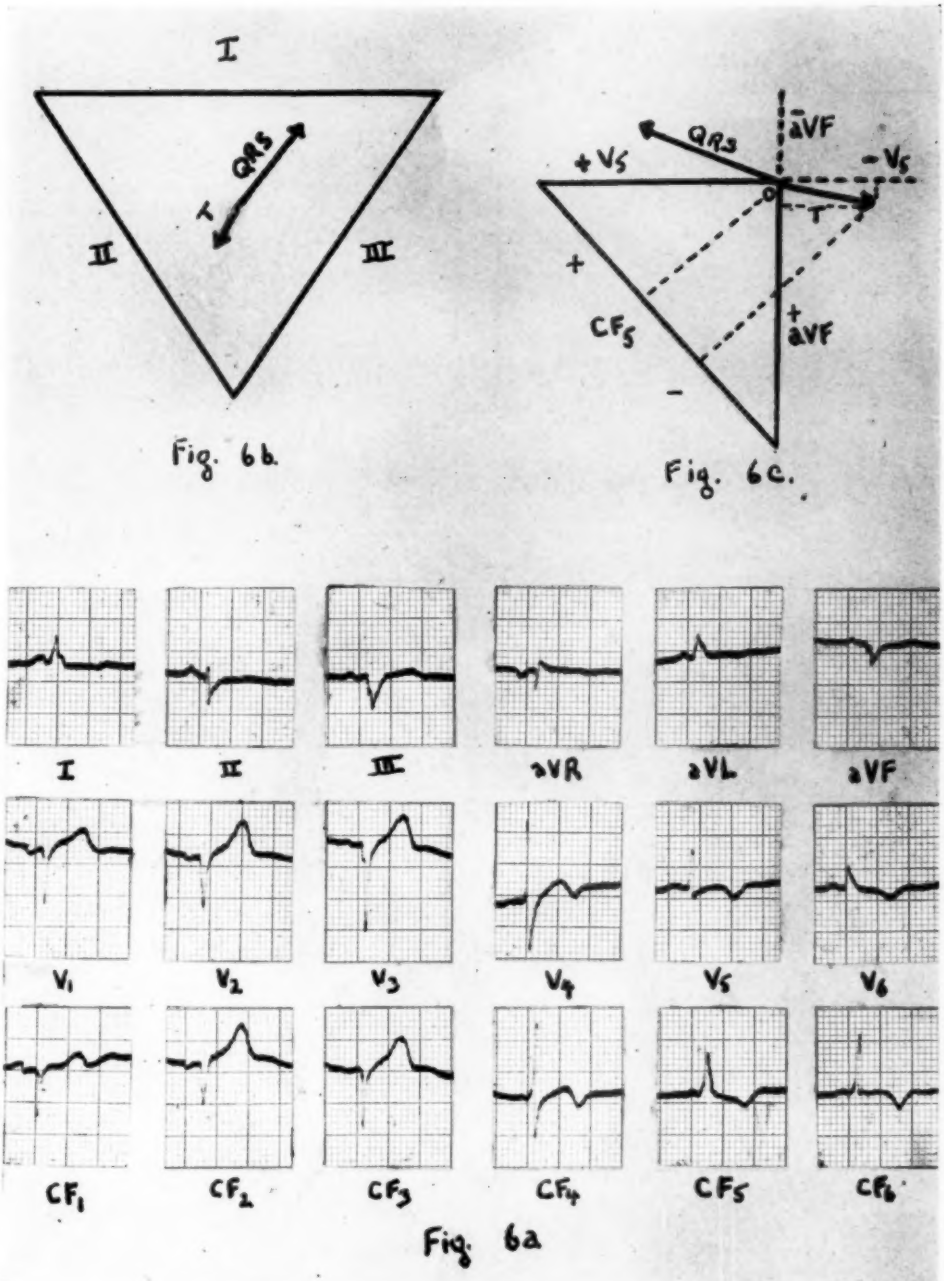

Fig. 6.—*a*, Frankly abnormal electrocardiogram of Case 6 showing the similarity between the CF and V precordial leads. *b*, Wide QRS-T angle approaching 180° in the frontal plane. *c*, QRS-T angle approaching 180° in the sagittal plane with the T vector perpendicular to aV_F.

This is true in the electrocardiogram of the usual normal vertical heart. That inversion of T waves in the CF leads must be interpreted cautiously in some vertical hearts can be seen from the case immediately following.

CASE 5.—This demonstrates the possibility that T-wave abnormalities in the CF leads may be less conclusive in vertical and semivertical hearts. Fig. 5,*a* presents the electrocardiogram of a man, age 50, whose first tracing in 1938, taken as part of a routine examination, showed an inverted T wave in Lead IV F although at no time were there signs or symptoms of organic heart disease. Repeated electrocardiograms have shown a stationary pattern and the tracing illustrated, taken in 1952, shows inverted T waves in the CF leads but upright T waves in the V leads. The absence of demonstrable cardiac pathology over a fourteen-year period would seem to indicate that the V leads correlate better with the clinical findings in this case than do the CF leads.

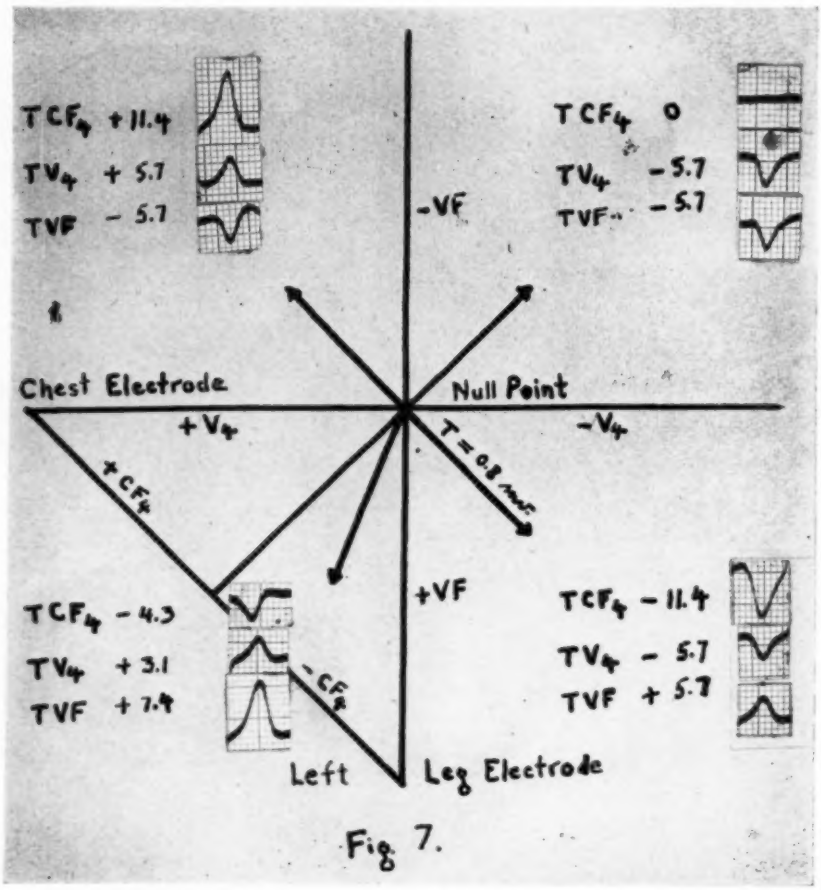

Fig. 7.—Schematic representation of the T vector having a magnitude of 0.8 mv. as it is projected in various segments of a 360° arc in the sagittal plane and the resulting deflections in Leads V_4, CF_4 and V_F.

Vectorial analysis of the electrocardiograms in this case shows that the QRS vector in the frontal plane is slightly to the positive side of Lead III, yielding a small upward deflection in Lead III. The T vector is slightly to the positive side of Lead I, yielding a small upward deflection in Lead I. The QRS-T angle in the frontal plane must be less than 60° (Fig. 5,*b*) and may be considered within normal limits. In the sagittal plane (Fig. 5,*c*) the QRS vector is chiefly upright in V_4 and similar though smaller in amplitude in CF_4 which shows a slightly deeper S wave. The QRS is upright and of moderate size in aV_F. Hence the QRS vector in the sagittal

plane may be considered to lie just to the positive side of the line representing CF_4. The T vector on the other hand, being equiphasic to inverted in CF_4, must lie just to the negative side of CF_4 as diagrammatically represented. The QRS-T angle is relatively narrow in both the frontal and sagittal planes. The acuity of this angle is of interest in the light of the negative clinical findings because this electrocardiogram would be considered abnormal by present criteria. The relationship between the QRS and T vectors in this case suggests that we are dealing with a semivertical position of the heart which has contributed to the inversion of T in CF_4 by orienting the T vector in a footward direction.

CASE 6.—Here is demonstrated the usual relationship of the T vector to the CF and V precordial leads in the presence of organic heart disease with left-axis deviation of QRS. Fig. 6,*a* presents an abnormal tracing which shows a left-strain pattern associated with an intraventricular conduction disturbance and a QRS duration of about 0.12 sec. The QRS-T angle is almost 180° (Fig. 6,*b*). However, because the T vector points posteriorly and is, therefore, almost perpendicular to aV_F in the sagittal plane (Fig. 6,*c*), the potential of T at the left leg is very small, approaching zero. Hence, T_{CF} and T_V deflections are almost identical. In this instance, then, the left leg electrode fails to alter the T_{CF} potentials, not because the left leg electrode is a remote and relatively indifferent electrode, as was once proposed, but because the T potential at the left leg is close to zero, the T vector being perpendicular to aV_F in the sagittal plane.

Fig. 7 is presented to show a number of the infinite, theoretically possible T-wave combinations as determined by the vector relationship, as the T vector rotates 360° in the sagittal plane. The diagram is self-explanatory. From the illustration it is apparent that the critical area in which T must always be negative in the CF leads and positive in the V leads is the inferior one-half of the right-angle triangle, which is in the left lower quadrant of the figure. An analagous figure may be constructed for the CR and V leads to demonstrate that there is a similar critical area of disagreement between these leads.

DISCUSSION

The question of the validity of Einthoven's hypothesis is part of the larger problem of the acceptability of the thesis of the symmetry of the electromagnetic field about the heart. If we can agree, as many observers do, that the variation in conductivity of the tissues about the heart is electrocardiographically negligible and if we can accept the idea that electrodes distant from the cardiac dipole record summation potentials from all surfaces of the heart, we must conclude that no electrocardiographic lead, whether bipolar or unipolar, has peculiar virtue. Indeed, by the same token, no electrocardiographic leads whether V or CF, CR or CL, or standard bipolar or unipolar limb leads give misleading information. They can only give different kinds of information or complementary information, and it depends upon the observer to interpret that information on the basis of his understanding of the distribution of potentials in a solid-conducting medium.

The V leads are unipolar leads which give accurate information concerning the precordial representation of the electromagnetic field surrounding the heart. The CF leads are bipolar leads which give additional information concerning the cardiac vectors as projected on a derivational lead connecting the explored precordial position and the left leg. Hence the CF leads may be used to measure the footward, as well as the precordial, deviation of the QRS or T vectors. Inverted T waves in the CF leads in the presence of upright T waves in the V leads, especially in horizontal hearts, may be a convenient measure of the obtuseness of the spatial QRS-T angle and yield the same kind of information, for the same physical reasons as when T_3 is taller than T_1 in a horizontal heart. This will have its greatest application in instances where the QRS-T angle approaches 90°

in either the frontal or sagittal plane as in the first three cases described. When the QRS-T angle approaches 180° as in the frankly pathologic last case there will be no problem since the V leads will show similar findings to the CF leads. In most instances, CF leads resemble the V precordial leads, not as was originally thought, because the left leg electrode is a remote and indifferent electrode, but because QRS and T potentials are frequently low at the left leg for positional reasons in horizontal and semihorizontal hearts, hence they contribute little to the potentials under the exploring electrode in the CF position. It may be anticipated then, if T_3 is taller than T_1, and hence T_{aVF} is tall, and some of the T waves in the precordial V leads are low, that the T waves in the same CF positions will be inverted. Indeed, since this may be seen at a glance, it may not be necessary to take CF leads at all, although this will continue to be a useful procedure for those who prefer to be guided by patterns. It would seem that the width of the QRS-T angle in space as determined by vector methods is a better measure of the abnormality of an electrocardiogram than the direction of the T wave in a given lead.

CONCLUSIONS

Several electrocardiograms are presented showing significant variation between the V precordial and CF leads. An explanation for this variation has been presented, based upon the algebraic relationship CF equals V minus VF and illustrated graphically in the frontal and sagittal planes. The electrocardiograms of a normal horizontal heart and that of a frankly pathologic heart showing no variation in the V and CF leads were illustrated for comparison. It is concluded that when T_3 is taller than T_1 and T_{aVF} is taller than some of the T waves in the V precordial leads, especially in the horizontal heart, it may be anticipated that the T waves in the same CF positions will be inverted. While this has diagnostic significance in the horizontal heart such criteria probably should be applied with caution to the vertical heart. Given the V and VF leads one can determine the pattern in CF. CR can similarly be determined from V and VR. Multiple positions of the indifferent electrode do not yield additional information.

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STUDIES ON THE MECHANISM OF VENTRICULAR ACTIVITY. XII. EARLY CHANGES IN THE RS-T SEGMENT AND QRS COMPLEX FOLLOWING ACUTE CORONARY ARTERY OCCLUSION: EXPERIMENTAL STUDY AND CLINICAL APPLICATIONS

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PRIOR to 1950, direct observation of electrical activity in the ventricles was accomplished primarily by means of epicardial and intracavity leads. Only during the last few years have reliable techniques been devised for recording intramural leads with electrodes located inside the ventricular wall, between the endocardium and epicardium. The application of these techniques in recent studies of normal ventricles,[1] chronic myocardial infarcts[2] and bundle branch block[3] has yielded new evidence concerning the genesis of normal and abnormal QRS patterns. From a clinical viewpoint, the S-T segment is no less important a component of the electrocardiogram than the QRS complex. S-T segment changes, associated with cardiac injury, often play a major role in the diagnosis of acute coronary occlusion, angina pectoris, and pericarditis. The present study was designed to elucidate such electrical effects by recording epicardial, intramural, and cavity leads from within and around regions of the dog's ventricle injured through coronary artery ligation.

LITERATURE

Theoretic Considerations.—Prevailing concepts of the electrophysiologic events responsible for injury effects are based upon Bernstein's membrane theory applied to cardiac muscle.[4] An injured region is defined as one which undergoes subnormal changes in the intensity of polarization owing to impairment of its ability to polarize or to depolarize.[5] If the injured muscle fails to polarize completely, it is negative with respect to uninjured muscle when the ventricle is in the diastolic (polarized) state. Conversely, if the injured muscle fails to depolarize completely, it is positive with respect to uninjured muscle when the ventricle is in the systolic (depolarized) state. In either event, a potential difference exists at the boundary between injured and uninjured muscle, giving rise to a flow of current across the boundary and an associated electrical field. The diastolic injury current resulting from incomplete polarization may be neutralized by a compensating current of opposite direction and equal magnitude so that it is not recorded in the electrocardiogram. S-T segment deviation is attributed by some workers to such a compensating current which flows unopposed during systole.[6] Others believe that a systolic injury current

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resulting from incomplete depolarization is at least partially responsible for S-T segment changes.[6] Since both the compensating current and the systolic injury current flow in the same direction, they would have an additive effect on the magnitude of the S-T segment displacement.

The preceding theory has been widely applied to explain the S-T segment displacements associated with various types of cardiac injury. During electrical systole, the potential difference at the boundary of injury is represented as a dipole oriented so that injured muscle is positive

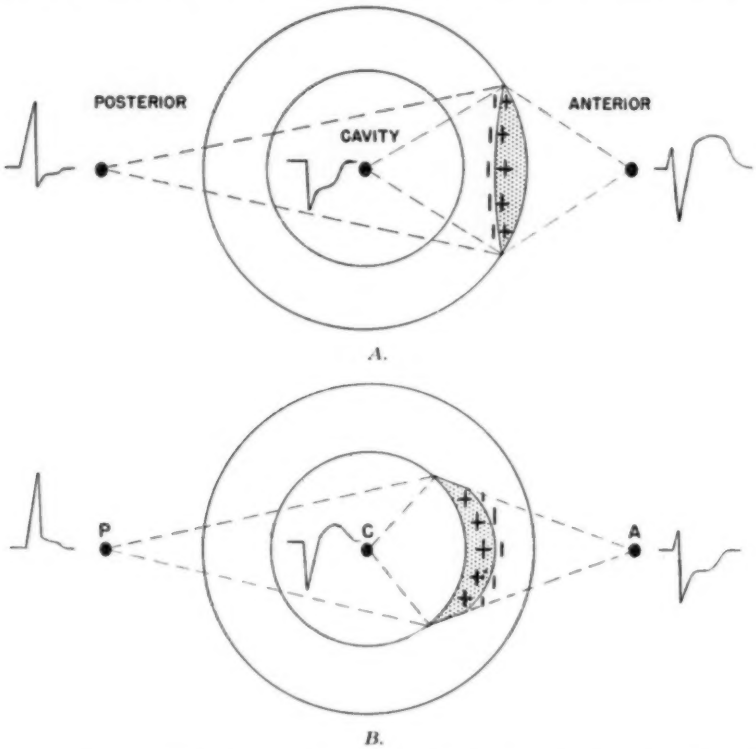

Fig. 1.—Diagrams illustrating classic theory of S-T segment displacement associated with localized ventricular injury. Injured region in anterior wall is stippled. Electrodes are located over anterior wall, in cavity, and over posterior wall opposite injury. Broken lines indicate angles subtended by electrodes with boundary between injured and uninjured muscle. A dipole is presumed to exist at the boundary of injury. During electrical systole, the positive pole of the dipole faces injured muscle while the negative pole faces uninjured muscle.

A, Subepicardial injury. Electrode over anterior wall subtends angle with injured side of boundary and therefore records elevated S-T segment. Electrodes in cavity and over posterior wall subtend angles with uninjured side of boundary; hence they register depressed S-T segments. S-T segment depression in cavity lead is greater than in posterior lead because cavity electrode is closer to injury and subtends greater angle with boundary.

B, Subendocardial injury. Electrode over anterior wall subtends angle with uninjured side of boundary while electrodes in cavity and over posterior wall subtend angles with injured side of boundary. Depressed S-T segment therefore occurs in anterior lead, elevated S-T segments in cavity and posterior leads.

while uninjured muscle adjacent to the boundary is negative. In the event of subepicardial or epicardial injury, the ventricular surface and precordium over the injured region face the positive side of the dipole. Unipolar leads from these sites should therefore present positive, or elevated, S-T segments. Conversely, the ventricular cavity and opposing wall face the negative side of the dipole and thus should yield negative, or depressed, S-T segments (Fig. 1*A*). In the event of subendocardial injury, the ventricular surface and precordium over the injured region face the negative pole of the dipole while the cavity and opposing wall face the positive pole. Accordingly,

electrodes over the injury should register depressed S-T segments while the cavity and opposing wall should yield elevated S-T segments (Fig. 1*B*). The downward S-T segment displacement associated with angina pectoris thus is supposed to result from subendocardial involvement. S-T segment changes in the bipolar limb leads can be shown by transposing onto the triaxial reference system a vector drawn through the center of the injured ventricle and the center of the injury as described by Bayley.[5] The vector is directed toward a subepicardial injury and away from a subendocardial injury.

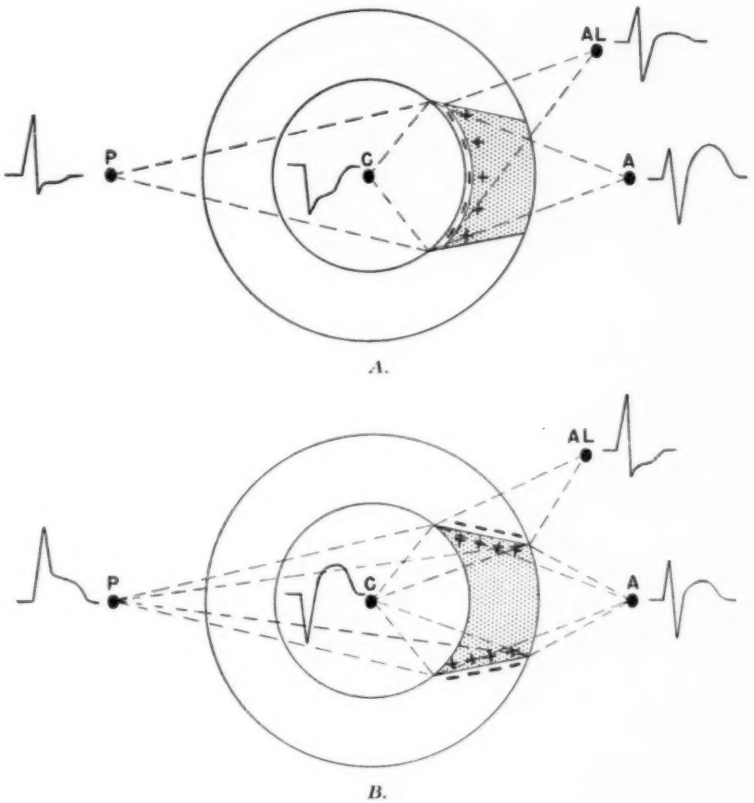

Fig. 2.—Diagrams illustrating alternative theories of S-T segment displacement associated with injury produced by coronary artery occlusion. Injured region in anterior wall (stippled) is broader subendocardially than at epicardium. Electrodes are over anterior wall (*A*), over anterolateral wall (*AL*), in cavity (*C*), and over posterior wall (*P*).

A, A thin layer of muscle bordering the cavity is assumed to escape anoxia. Dipole at boundary of injury thus is oriented as in subepicardial injury (Fig. 1*A*), the positive pole facing the anterior surface during electrical systole while the negative pole faces the cavity and posterior wall. Electrode *A* over anterior wall subtends wide angle with injured side of boundary and therefore records markedly elevated S-T segment. Electrode *AL* over anterolateral wall subtends smaller angle with injured side of boundary; hence it registers less marked S-T segment elevation. Electrodes in cavity and over posterior wall subtend angles with uninjured side of boundary and therefore record depressed S-T segments.

B, Injury presumably involves all layers of wall from endocardium to epicardium. Dipole is represented at lateral boundaries of injured region. As in Figs. 1*A*, 1*B* and 2*A*, the positive pole faces injured muscle during electrical systole while the negative pole faces uninjured muscle. Electrode *A* over anterior wall, electrode *C* in cavity, and electrode *P* over posterior wall subtend angles with injured side of boundaries. Elevated S-T segments therefore appear in anterior, cavity, and posterior leads. Since the cavity electrode is closest to the injury and subtends the widest angles with the boundaries, it records the greatest degree of S-T segment elevation. Electrode *AL* over the anterolateral wall subtends a wide angle with the uninjured side of the boundary and thus registers a markedly depressed S-T segment.

Some difference of opinion exists concerning the theoretical explanation of S-T segment displacement following typical coronary artery occlusion. Since injuries resulting from occlusion characteristically are broader in the inner ventricular layers than at the epicardium, they are primarily of the subendocardial type which should yield depressed S-T segments over the injured ventricle. Bayley, however, has cited anatomic evidence that a thin layer of subendocardial muscle adjacent to the cavity escapes anoxia.[5] Under such circumstances, injuries extending to the ventricular surface would be of the subepicardial type which yield elevated S-T segments in leads from overlying sites and depressed S-T segments in leads from the cavity and opposite wall (Fig. 2*A*). Barker, on the contrary, considered that many injuries during the acute stage of coronary occlusion involve all layers of the ventricle. He attributed the electrical effects of these transmural injuries to incomplete depolarization which gives rise to a dipole at the lateral boundaries between injured and uninjured muscle.[7] According to this hypothesis, elevated S-T segments would be registered by electrode subtending angles with the injured side of the transmural boundaries while depressed S-T segments would appear if the electrodes subtend angles with the uninjured side of the boundaries (Fig. 2*B*).

Experimental Observations.—Considerable experimental evidence has been reported concerning the electrocardiographic effects of injury produced by coronary artery ligation or by direct myocardial trauma. In accordance with the hypotheses of both Bayley and Barker as well as with clinical experience, elevated S-T segments were registered over regions to which the blood supply had been curtailed by ligating appropriate coronary arteries.[8-11] Hellerstein and Liebow[8a] and Sodi-Pallares[8b] observed that the S-T segment elevation was associated with a delay in the peak of the R wave, an increase in amplitude of the R wave, and a decrease in amplitude of the S wave. Sodi-Pallares attributed the QRS changes to a functional blocking of depolarization in the injured region. Pruitt and Valencia[9] recorded elevated S-T segments in cavity leads directly under, as well as in epicardial leads directly over, injuries produced by coronary artery ligation. As interpreted by Wilson and associates,[6] this observation indicates that the injury involves muscle adjacent to the cavity and therefore is not of the subepicardial type. Leads recorded over uninjured portions of the ventricle either near or opposite injured regions showed isoelectric S-T segments in some instances[10] and depressed S-T segments in other cases.[10,11]

Subepicardial injuries produced by application of chemicals or trauma, like transmural injuries produced by coronary artery ligation, consistently yielded elevated S-T segments in leads registered over the injured muscle.[9-11] Isoelectric[9] or depressed[10,11] S-T segments were found in tracings from the cavity beneath the subepicardial injuries and from uninjured sites on the involved or opposite wall. Wolferth and associates[11] observed that the specific characteristics of the S-T segment differed with the method used to injure the epicardium. Both Wolferth and associates[11] and Kisch and co-workers[12] attempted to produce subendocardial injuries by traumatizing the endocardium. They reported the frequent occurrence of isoelectric S-T segments in leads over the site of trauma[11] and in limb leads[12] which they attributed to the distance between the injured endocardium and the recording electrodes. An alternative explanation was proposed in a previous report from this laboratory[1] describing the injury effects incident to insertion of intramural electrodes into the ventricular myocardium. Comparable degrees of trauma inflicted by the electrode always elicited much more marked injury effects from the outer layers than from the inner layers. This observation was regarded as evidence that a limited capacity of the inner layers to respond electrically to trauma, rather than the distance of these layers from the epicardium, might account for the absence of S-T segment changes over subendocardial injuries.

In the initial and major part of the paper, acute experiments are discussed in which observations were made on the nature of the S-T segment elevation during the first thirty minutes after acute coronary occlusion. In the latter part of the paper, preliminary observations are presented on more prolonged experiments in which S-T segment depression occurred.

MATERIALS AND METHODS

A total of twenty-one dogs weighing from 10 to 16 kilograms each was used in the study. The animals were anesthetized with pentobarbital sodium administered intravenously in doses averaging 25 to 30 mg. 1 kg. of body weight. A transsternal incision was made in the fifth intercostal space and the third and fourth ribs removed bilaterally. Wide exposure of the heart was accomplished by retraction. The pericardium was opened and sutured to the chest wall to form a supporting sling for the heart. An electric pump respirator maintained artificial respiration.

After electrodes had been situated in the ventricle as described later, control electrocardiograms were made. A suture was then drawn tight around the left anterior descending coronary artery in order to cut off the blood supply to the region containing the electrodes. The site of ligature varied with the individual pattern of large collaterals in each dog. Within a few minutes after the suture was tied, marked discoloration of a portion of the ventricular surface became apparent. The discolored area ballooned outward during systole, indicating that contractility of the underlying wall was impaired. Although these changes were grossly visible, they could be seen most clearly in high-speed color cinematographs of the ventricle. Thus the surface of the injured region was clearly delineated both by its cyanotic color and by its abnormal motion.

Direct leads from the epicardial surface were made with saline-soaked cotton-tipped electrodes composed of platinum wire. In sixteen experiments, at least one electrode was sutured to the epicardium within the injured area. Epicardial electrodes also were sutured 1 or 2 mm. from the injured area on eight occasions. A movable epicardial electrode was employed in eight animals to explore the entire ventricular surface within and around the injured area. Leads from the posterior surface were made in six instances.

Simultaneously with the epicardial leads, intramural leads from different levels of the ventricles were recorded by means of sharp-tipped plunge electrodes. These tiny electrodes were inserted into the ventricular wall at right angles to the epicardium immediately subjacent to the sutured epicardial electrodes (see diagram in Fig. 3). By marking the plunge electrodes at 2 mm. intervals, the distance of their recording points from the epicardium could be determined as they were pushed into the ventricle. A definite increase in resistance was felt when the tip of an electrode reached the endocardium, followed by an abrupt cessation of electrode-induced injury effects as the endocardium was pierced and the cavity entered. Subendocardial leads thus could be recorded at any desired distance from the endocardium by either of two methods. (1) The electrode was pushed through the wall until it contacted the endocardium, as manifested by increased resistance, then withdrawn a given distance to the desired level. (2) The electrode tip was placed in the cavity as established by the absence of injury effects, then withdrawn until injury effects abruptly reappeared at the endocardium, and further withdrawn a given distance to the desired level. The depths at which intramural tracings were made ranged from 2 mm. below the

epicardium to within ½ mm. of the endocardium. Injury effects always appeared in the intramural tracings immediately after insertion of the electrodes but disappeared or reached a minimum within 2 to 10 minutes.

In most experiments, three single plunge electrodes were used to record simultaneous tracings from subepicardial, midmural, and subendocardial levels of the injured region. The single plunge electrodes consisted of 20-mil tempered silver wire, chlorided and insulated throughout except for a bare tip or side opening approximately ½ mm. in diameter. A compound tungsten electrode with three recording tips was substituted for the single electrodes in several instances.[13]

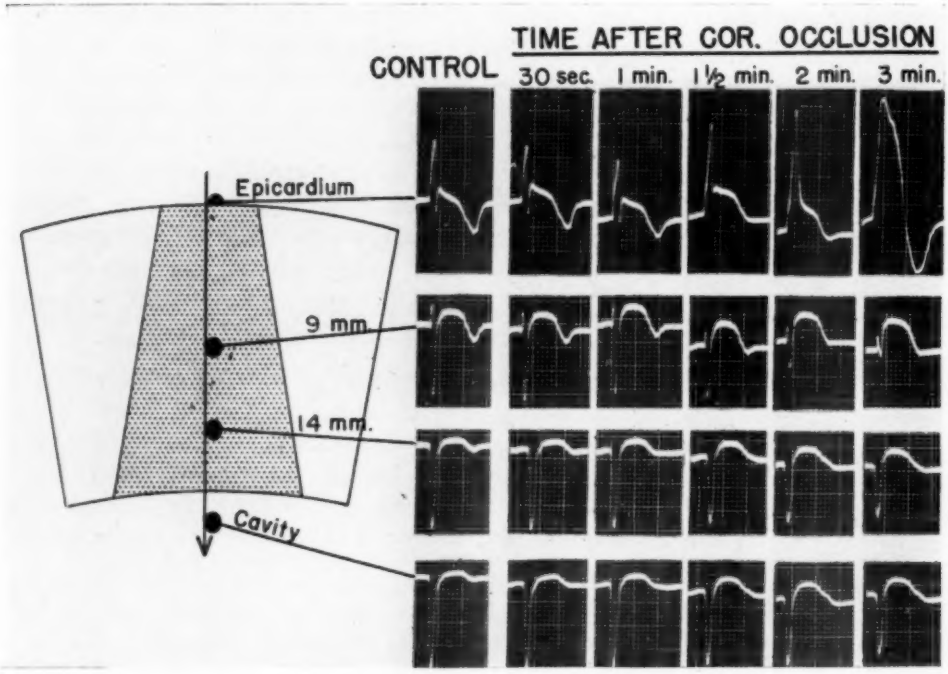

Fig. 3.—Left, Diagram showing situation of electrodes in ventricle injured by coronary artery ligation. Injured muscle is stippled. Black line indicates path of plunge electrodes, black dots represent location of lead points. Right, Tracings from electrodes situated as shown in diagram. Electrocardiograms recorded on Sanborn Polyviso at paper speed of 50 mm. per second. Slight S-T segment elevation in control tracings is residual effect of electrode trauma. Before coronary artery ligation, Rs wave is recorded in epicardial lead, rS wave in intramural lead from 9 mm. depth, pure QS waves from 14 mm. depth and from cavity. Progressive elevation of S-T segment and decrease in amplitude of S wave occurs in all leads after coronary artery ligation. Upstroke of epicardial R wave increases in amplitude and duration, finally merging with S-T segment to form monophasic curve. Note that changes in S-T segment and QRS complex are greatest in epicardial lead, considerably less marked in lead from 9 mm. depth, slight in leads from 14 mm. depth and cavity.

Each compound electrode was composed of a completely insulated central shaft 5-mil in diameter and three lengths of 2-mil wire insulated throughout except at the tip. The 2-mil wires were cemented to the central shaft so that their tips lay 6 to 10 mm. apart. Leads from the underlying ventricular cavity as well as from subendocardial, midmural, subepicardial, and epicardial levels of the injured region were registered in most instances. Injury effects at all levels from ventricular surface to cavity thus could be recorded simultaneously.

The disturbance of blood supply produced in the present experiments was such that subendocardial injuries should have developed adjacent to the transmural injuries seen at the epicardial surface. In order to explore the subendocardial injuries, plunge electrodes were inserted a few millimeters beyond the margins of the injured epicardial area in eight animals. Midmural and subendocardial leads from these electrodes were recorded simultaneously with a lead from the directly overlying uninjured epicardium (see diagram in Fig. 7). A second experiment designed to explore intramural muscle adjacent to the transmural

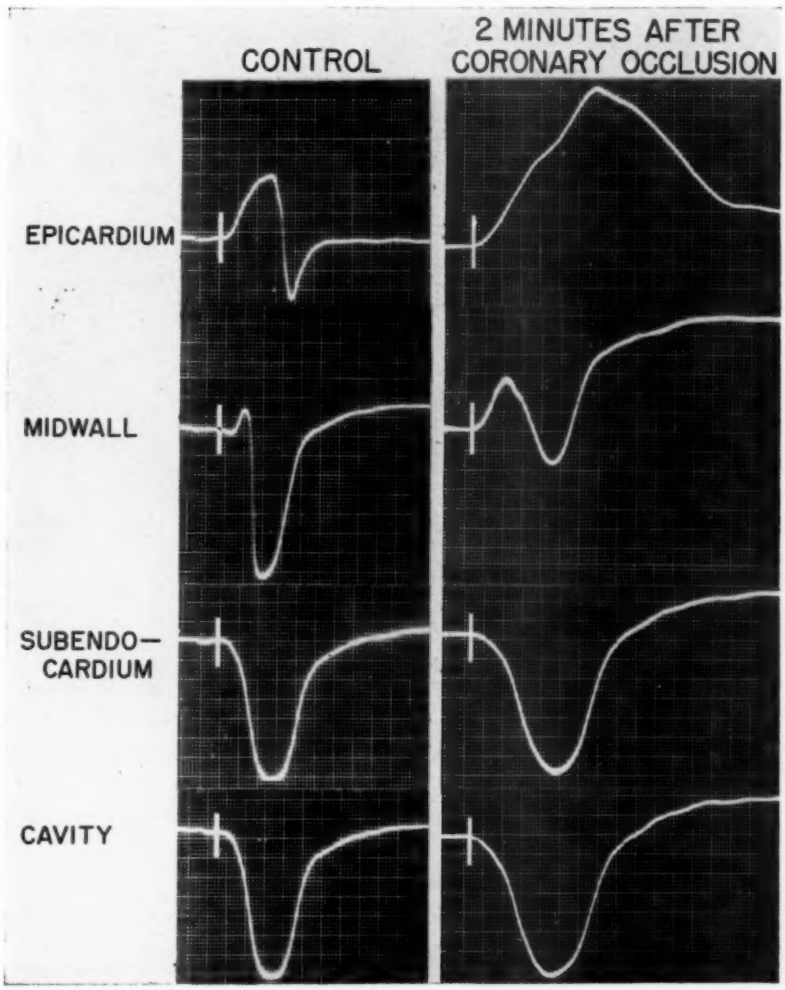

Fig. 4.—Epicardial, intramural, and cavity leads from left ventricle recorded on cathode-ray oscillograph. Intramural and cavity lead points were directly beneath epicardial lead point as shown by diagram in Fig. 3. Subendocardial lead point was ½ mm. above endocardium. Interval between heavy time lines equals 0.008 second. Left, Control tracings. Right, Same leads recorded 2 minutes after coronary artery was ligated to produce anoxia of region containing electrodes. S-T segment is elevated in all leads, but the degree of elevation decreases progressively from epicardium to cavity. R wave in epicardial lead has risen to merge with elevated S-T segment, forming large monophasic curve. S wave in midmural lead is markedly reduced in amplitude.

injuries consisted of inserting several plunge electrodes parallel to one another at 2 to 3 mm.-intervals along a line extending from the center to several millimeters beyond the margins of the injured epicardial area. As shown by the 2 mm.-markings on the electrodes, the several recording points in the ventricle were equidistant from the epicardium between midmural and subendocardial levels (see diagram in Fig. 8). This experiment was performed in two animals.

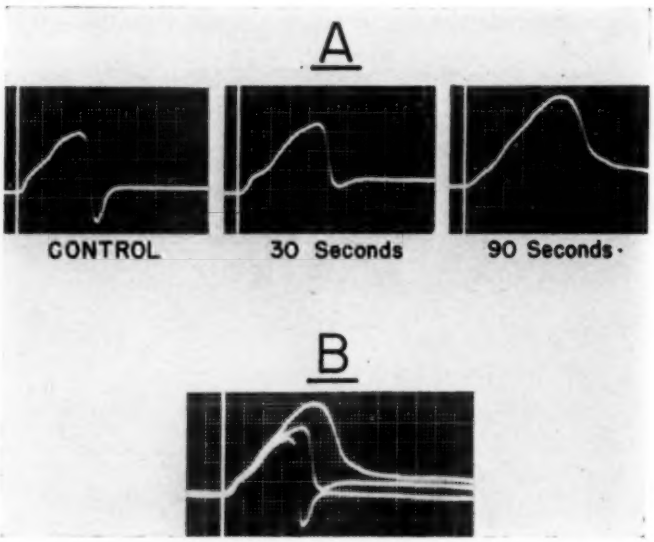

Fig. 5.—Epicardial lead recorded on cathode-ray oscillograph before and after coronary artery ligation. Interval between heavy time lines equals 0.0085 second. *A*, Rs wave and isoelectric S-T segment appear in control tracing. Area around electrode assumed cyanotic color after coronary artery ligation while R wave gradually increased in height, peak of R wave became delayed, and S wave disappeared. *B*, Three tracings in *A* have been superimposed. Note that upstroke of R wave remains unchanged in slope as progressive QRS alteration occurs.

Tracings were registered on a 4-channel Sanborn Polyviso Electrocardiograph at a paper speed of 50 mm./sec. and on a DuMont dual-beam cathode-ray oscillograph. A Fairchild Oscillo-Record camera and two Grass preamplifiers were used with the oscillograph. The over-all frequency response of the oscillographic system was accurate to approximately 10,000 cycles per second.

RESULTS

As in previously reported experiments,[1,2a] S-T segment elevation of gradually diminishing amplitude occurred in intramural leads after insertion of the sharp-tipped plunge electrodes. The maximum amplitude of the S-T segment was always greater in leads from the outer ventricular layers than in leads from the inner layers. These injury effects as well as those elicited by suturing the epicardial electrodes were allowed to disappear or reach a minimum before the coronary artery was ligated.

Control Tracings.—Leads from the epicardial surface before coronary artery ligation exhibited R waves followed by S waves and isoelectric or slightly elevated S-T segments. The T waves usually were inverted. Intramural leads from

subepicardial levels presented smaller R waves and larger S waves than the epicardial leads but otherwise appeared similar. As the distance from the epicardium increased, the initial R wave in the intramural leads diminished rapidly in width and amplitude, becoming imperceptible at midventricular levels. The inner one-third of the ventricular wall as well as the cavity yielded pure QS waves. These observations confirm those described in a previous report on intramural depolarization potentials in normal ventricles.[1,2a]

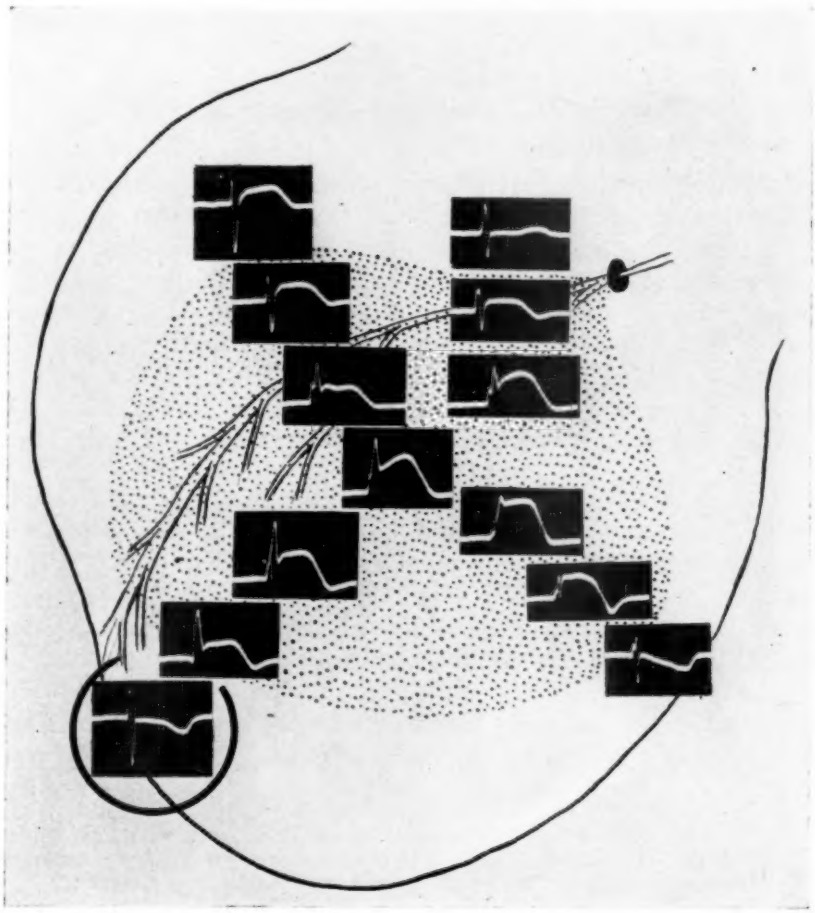

Fig. 6.—Epicardial leads from injured area and adjacent normal-appearing muscle. Black circle in diagram of coronary shows location of ligature. Stippling represents cyanosis which developed after ligation, delineating injured epicardial area. S-T segment elevation is most marked in leads from center of injury and decreases gradually toward the margins. Isoelectric S-T segments are recorded from normal-appearing epicardium outside the margins of injury. The circled complex in the lower left-hand corner is recorded from the posterior surface and illustrates reciprocal S-T segment depression.

Epicardial Leads After Coronary Artery Ligation.—Elevation of the S-T segment in epicardial leads from the injured area began within 30 to 60 seconds after the coronary artery was tied and reached a maximum within 5 to 7 minutes. The epicardial complex exhibited a gradual change of configuration, culminating in the appearance of a monophasic curve in twelve animals (Figs. 3 and 4).

Notches or plateaus on the downstroke were visible throughout the period of observation in the remaining four cases.

Concurrently with the S-T segment elevation in epicardial leads from the injured area, a progressive alteration of the depolarization complex occurred. The S wave became shallower and finally disappeared. An increase in amplitude and a delay in the peak of the R wave was consistently observed; the increase in amplitude ranged from 2.2 to 20 mm. or from 31 to 1,000 per cent while the delay of the peak ranged from 0.01 to 0.03 sec. in the sixteen cases studied. No change in slope of the ascending limb of the R wave was perceptible; rather, the increased length of the upstroke appeared responsible for the delay in the peak of the R wave. The evolution of these QRS alterations was most clearly observed in oscillographic tracings (Fig. 5).

Exploration of the anterior surface revealed a gradual decrease in height of the S-T segment as the electrode was moved from the center of the injured area toward the margins. Normal muscle immediately surrounding the injury as well as more distant epicardium yielded isoelectric S-T segments (Fig. 6). On no occasion was a depressed S-T segment recorded from the anterior surface of the injured ventricle during the first half hour following acute coronary occlusion. Slight to moderate depression of the S-T segment often occurred in epicardial leads from the posterior surface. The circled complex in the lower left-hand corner (Fig. 6) is from the posterior surface and shows slight S-T depression.

Intramural and Cavity Leads After Coronary Artery Ligation.—Within 30 to 60 seconds after occlusion, the S-T segment in intramural leads from the injured region began to rise. This change started simultaneously with the S-T segment elevation in epicardial leads from overlying sites but progressed less rapidly and was of lesser magnitude. The height of the S-T segments varied inversely with the distance of the lead-point from the epicardium; elevation was most marked in epicardial leads, somewhat less pronounced in subepicardial, moderate in midmural, and slight in subendocardial leads. Cavity leads recorded directly beneath the injured region exhibited elevated S-T segments similar to or lower than those in the subendocardial tracings (Table I and Figs. 3 and 4).

TABLE I. MAXIMUM CHANGE IN QRS COMPLEX AND S-T SEGMENT DURING INITIAL STAGE OF INJURY PRODUCED BY CORONARY ARTERY LIGATION*

LEVEL OF LEAD POINT	QRS COMPLEX			S-T SEGMENT (MM.)
	CONTROL	DELAY IN PEAK (SEC.)	CHANGE IN AMP. OF PEAK (MM.)	
Epicardium	Rs	0.018	+17.2	+10.8
Subepicardium	RS	0.014	+ 6.8	+ 9.1
Midwall	QS	0.0	− 7.0	+ 4.2
Subendocardium	QS	0.0	− 4.7	+ 3.0
Cavity	QS	0.0	− 5.6	+ 2.7

*Average figures for 16 experiments.

A progressive decrease in amplitude of the S wave began simultaneously with the S-T segment elevation in intramural and cavity leads. Shortly after the onset of these changes, the upstroke of the R waves recorded from the outer ventricular layers began to increase gradually in amplitude and duration. As observed with respect to S-T segment elevation, these QRS changes decreased progressively in magnitude from epicardium to cavity. Thus the RS waves recorded in control tracings from the subepicardial level were no longer recognizable several minutes after coronary artery ligation while the QS waves in subendocardial and cavity leads appeared only slightly altered.

The assumption that injuries produced by coronary artery ligation are broader subendocardially than epicardially was confirmed in the eight instances in which plunge electrodes were located a few millimeters beyond the margins of injured epicardial areas. Rising S-T segments appeared in the subendocardial and midural leads after ligation, establishing the presence of injury at these levels.

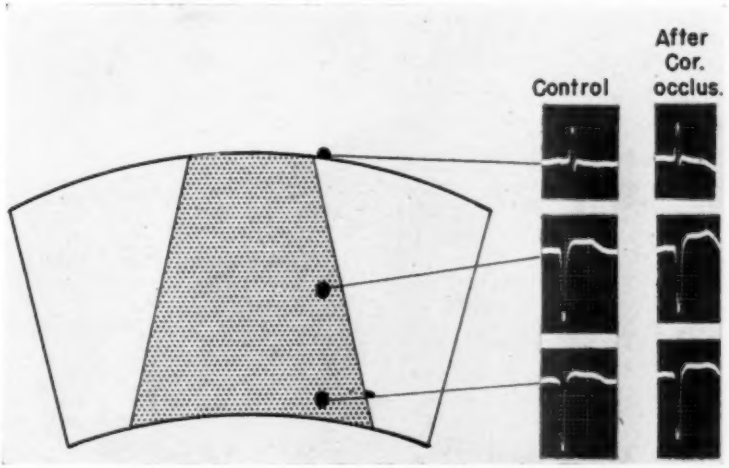

Fig. 7.—Left, Diagram showing location of electrodes in experiment designed to explore region of subendocardial injury adjacent to transmural injury. Epicardial electrode is placed on normal-appearing muscle immediately outside margin of cyanotic area. Black dots represent lead points of plunge electrodes inserted directly beneath epicardial electrode. Right, Simultaneously recorded tracings from electrodes located as shown in diagram. Midmural and subendocardial leads present S-T segment elevation after coronary artery ligation, indicating that injury extends intramurally beneath normal-appearing epicardium. S-T segment in epicardial lead from directly overlying site remains isoelectric.

The S-T segments in tracings from the overlying epicardium remained isoelectric (Fig. 7). In no instance were depressed S-T segments recorded from normal-appearing epicardium over the subendocardial injuries in the period of observation immediately following acute coronary occlusion.

S-T segment depression also failed to occur in leads from intramural sites lateral to the boundaries of injured regions. Instead, a gradual transition from elevated to isoelectric S-T segments was registered at successive lead-points along a line extending from the center of the injury parallel to the epicardium at intramural levels (Fig. 8). The degree of S-T segment elevation in simultaneous leads varied inversely with the distance of the electrode from the center of injury, finally becoming imperceptible in tracings recorded beneath normal-appearing

epicardium several millimeters beyond the injured epicardial area. Hence the injured regions appeared to be several millimeters broader at deeper levels than at the ventricular surface. Intramural leads from outside the lateral boundary of injury presented isoelectric S-T segments. Uninjured muscle within the anterior wall, like uninjured portions of the anterior surface, thus failed to yield S-T segment depression.

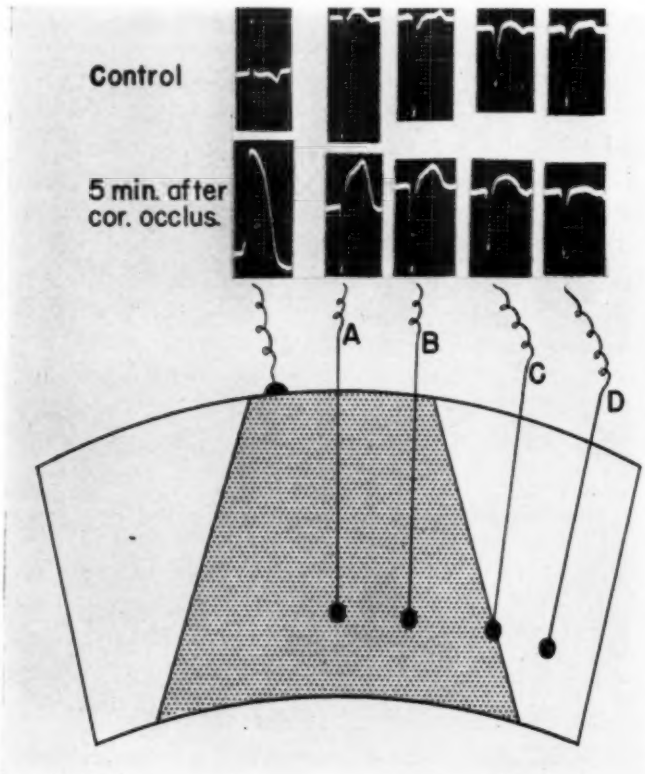

Fig. 8.—Simultaneously recorded intramural leads from plunge electrodes situated as shown in diagram. Purpose of experiment is to determine if S-T segment changes occur at intramural levels outside boundary of injury. Black lines represent paths of electrodes, black dots correspond to lead points. Electrode *A* was inserted through center of cyanotic epicardial area, electrode *B* near margin of cyanotic area, electrodes *C* and *D* through normal-appearing epicardium. Epicardial lead from injury shows marked S-T segment elevation 5 minutes after coronary artery ligation. S-T segment is moderately elevated in intramural lead *A* from center of injury, somewhat less elevated in intramural lead *B*, slightly elevated in lead *C* and isoelectric in lead *D*. As in Fig. 6, gradual transition from maximal S-T elevation to S-T isoelectricity occurs as distance from center of injury increases. Depressed S-T segments do not appear in lead from outside boundary of injury.

DISCUSSION

S-T Segment Displacement.—The occurrence of S-T segment elevation over injuries involving the ventricular surface was a constant result of the present experiments. This observation is in accordance with a wealth of previously reported experimental and clinical data concerning the acute effects of coronary artery occlusion. Although the empirical evidence thus appears consistent, the theoretical explanation of S-T segment elevation following coronary occlusion

remains a subject of controversy. As discussed earlier, some authorities[5] believe that a thin layer of muscle adjacent to the cavity escapes anoxia, in which case a dipole may be represented at the boundary between the uninjured subendocardial layer and overlying injured muscle. Other investigators[6,7] propose that all layers of the ventricular wall undergo injury, giving rise to a dipole at the lateral boundaries between injured and uninjured muscle. In either event, the dipole is oriented so that injured muscle is positive during systole while uninjured muscle is negative. Electrodes facing the injured side of the boundary thus should record elevated S-T segments while electrodes facing the uninjured side of the boundary should register depressed S-T segments. Since electrodes over injuries reaching the ventricular surface would face the injured side of either a subendocardial or a transmural boundary of injury, either of the preceding hypotheses would account for the S-T segment elevation commonly associated with coronary artery occlusion. The following considerations, however, suggest that neither hypothesis can be applied to the experimental data reported in this paper.

If a thin layer of muscle bordering the ventricular cavity escaped anoxia after occlusion, this layer as well as the cavity directly beneath the involved region would face the uninjured side of the boundary of injury (Fig. 2*A*). Electrodes at these sites should therefore record depressed S-T segments. Conversely, the overlying muscle facing the injured side of the boundary should yield elevated S-T segments. During the present study, subendocardial leads were registered as little as ½ mm. from the cavity directly beneath grossly injured portions of the ventricular surface. The subendocardial tracings always showed elevated S-T segments (Fig. 4). Moreover, cavity leads recorded directly beneath the injuries also presented elevated S-T segments (Figs. 3 and 4), confirming the observation of Pruitt and Valencia.[9] An abrupt transition from positive to negative S-T segments, such as should occur if a dipole were present at a subendocardial boundary of injury, was never seen in leads from successively deeper levels of the ventricle. Instead, the amount of S-T segment elevation decreased gradually from epicardium to cavity, indicating that the entire thickness of the ventricular wall was injured.

If a dipole were present at the lateral boundaries of an injured region, injured muscle would face the positive pole of the dipole during systole and therefore would yield elevated S-T segments. Uninjured muscle adjacent to the boundaries, on the other hand, would face the negative pole and thus should yield depressed S-T segments (Fig. 2*B*). During the present study, epicardial electrodes within the injured region registered elevated S-T segments which decreased in amplitude as the lead-point was moved away from the center of injury. Epicardial electrodes at all sites on the anterior surface outside the boundary of injury recorded isoelectric S-T segments during the early period of observation following coronary artery occlusion (Fig. 6). Similarly, intramural tracings from lead-points in a line parallel to the epicardial surface showed a gradual transition from marked S-T segment elevation to S-T segment isoelectricity as the distance between the electrode and the center of the injured region increased (Fig. 8). Again, no abrupt change from positivity to negativity was recorded at the boundary of injury. Only on the posterior surface opposite the injured

region were depressed S-T segments sometimes registered. Hence a dipole could not be located at the lateral boundary of injury either on the epicardium or at intramural levels of the injured wall.

The foregoing observations suggest that the S-T segment elevation recorded during coronary occlusion may not be related to a dipole at the boundary between injured and uninjured muscle. These observations further indicate that the S-T segment depression associated with coronary disease does not result from subendocardial injury as is generally supposed. Injuries produced by coronary occlusion, like infarcts, presumably are more widespread at subendocardial levels than at the epicardium. Under such circumstances, the epicardial surface of a transmural injury would be circumscribed by an area of uninjured muscle directly overlying injured subendocardium. If depressed S-T segments occurred over subendocardial injuries, they should thus have appeared in epicardial leads from immediately outside the margins of the injured areas seen in the present experiments. Actually, these leads presented isoelectric S-T segments throughout the period of observation following coronary artery ligation (Fig. 6). The presence of subendocardial injuries contiguous to the transmural injuries was confirmed on eight occasions by the occurrence of S-T segment elevation in subendocardial leads recorded directly beneath normal-appearing epicardium. Epicardial leads over the subendocardial injuries showed isoelectric S-T segments (Fig. 7). Once again, therefore, a change from positivity to isoelectricity rather than a dipole was found at the boundary between injured and uninjured muscle.

During the past four years, several thousand intramural leads from over five hundred dog's ventricles have been recorded in this laboratory. A constant finding was that insertion of plunge electrodes into the myocardium elicited much more marked injury effects from the outer ventricular layers than from the inner layers. The present experiments establish that injuries produced by coronary artery ligation, like those resulting from electrode trauma, yield a progressively decreasing degree of S-T segment elevation from epicardium to endocardium. Injection of M/5 potassium chloride into various levels of the myocardium from epicardium to endocardium yielded the same results. Throughout the 30-minute period of observation after coronary artery ligation, the S-T segment elevation recorded from regions of transmural injury was of greatest amplitude in epicardial leads, somewhat less in leads from the outer ventricular layers, relatively slight in leads from the inner layers, and minimal in cavity leads. Similar results were obtained during two other series of experiments, one in which eight animals were studied 6 to 48 hours after coronary artery ligation[14] and another in which five animals with bundle branch block were observed immediately after coronary ligation.[15] Again, multiple intramural leads recorded after the subsidence of electro-induced injury effects exhibited progressively decreasing S-T segment elevation from epicardium to endocardium. This gradient of S-T segment change cannot be related to the distribution of the injury, since several injured regions were shown to include a greater area subendocardially than epicardially (Fig. 7 and 8). Moreover, infarcts characteristically increase in breadth with the distance from the epicardium indicating that the degree of damage resulting from anoxia is greatest at deeper intramural levels. Both the extent and the severity of myocardial involve-

ment incident to coronary artery occlusion thus diminish in an endocardial-to-epicardial direction while the electrical effects of injury, represented by S-T segment displacement, diminish in the opposite direction. The theoretical applications of this observation will be illustrated with respect to S-T segment changes in precordial and limb leads from patients with coronary artery disease. Although the following discussion is limited to injuries involving the anterior wall of the left ventricle, the same principles may be assumed to apply regardless of the location of the injury.

One of the theoretical problems often encountered in clinical electrocardiography concerns the displaced S-T segments recorded from patients during the early stages of infarction. For example, when the anterior wall is involved, such patients frequently show elevated S-T segments in anterior chest leads and in limb Lead I, while depressed S-T segments occur in chest leads over the posterior wall, in Lead aV_F, and in limb Lead III. As pointed out by Bayley,[5] the direction of the vector is comparable to that of a subepicardial injury involving the anterior wall, although subsequent pathologic examination usually reveals more extensive infarction of the subendocardial layers. If muscle immediately adjacent to the cavity remains intact, as in the histologic descriptions quoted by Bayley, these findings may be reconciled with the dipole theory reviewed earlier (Fig. 2*A*). Considerable evidence, however, has been cited to show either that an uninjured layer bordering the cavity seldom exists after occlusion or that the electrical effects of such a layer would not be of sufficient magnitude to affect clinical tracings.[7] The alternative hypothesis which attributes S-T segment displacement to a dipole at the lateral boundaries of the injured region likewise fails to explain many clinical cases. According to this hypothesis, precordial electrodes over the anterolateral wall not directly facing transmural portions of the injury would subtend angles with the uninjured side of the boundary and therefore should record depressed S-T segments (Fig. 2*B*, electrode *AL*). Conversely, electrodes over the injury or over the posterior wall opposite the injury would subtend angles with the injured side of the boundary and hence should register elevated S-T segments (Fig. 2*B*, electrodes *A* and *P*). A reciprocal relationship thus would exist between the S-T segment displacement recorded directly over or opposite the injury and that recorded lateral to the injury. Actually, however, the S-T segment changes associated with anterior infarction generally show a reciprocal relationship between the anterior and posterior walls. Elevated or isoelectric S-T segments occur in all anterior leads while depressed or isoelectric S-T segments occur in posterior leads. Since precordial Leads V_1 and V_6 often face almost opposite aspects of the heart, S-T segment elevation in V_1 may be found with S-T segment depression in V_6. Apparently, then, neither of the two commonly accepted explanations of S-T segment displacement is applicable to a large proportion of patients with coronary artery disease. As illustrated in Fig. 9, the experimental findings described in the present paper suggest a third hypothesis which may account for previously puzzling features of these cases. In this instance we have only considered the depression as a reciprocal phenomenon. In actual practice, however, S-T depression closer to the S-T elevation may occur and is discussed later.

A transmural injury of the anterior wall of the left ventricle is represented diagrammatically in Fig. 9. In accordance with the results of the present experiments, the injured region and underlying cavity are shown to be positive during systole while adjacent uninjured muscle is isoelectric. The progressive decrease in size of the positive signs from epicardium to cavity and from the center to the margins of the injured region correspond to the gradient of S-T segment elevation

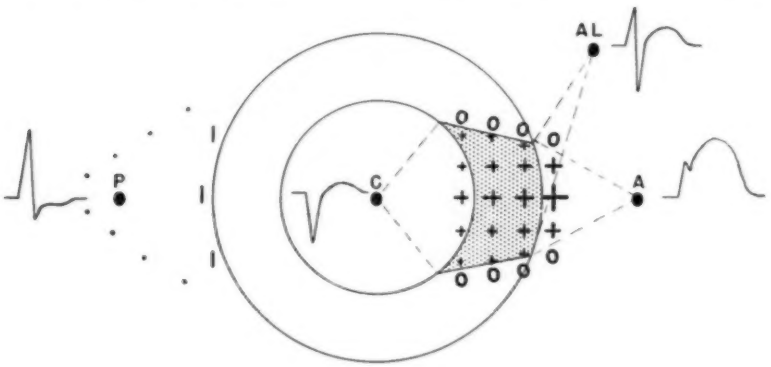

Fig. 9.—Diagram showing actual distribution of potentials in injured ventricle after coronary artery occlusion as recorded by means of epicardial, intramural, and cavity leads. Injured region in anterior wall is stippled. Plus (+), zero (0), and minus (−) signs represent local potentials recorded during electrical systole in direct leads from injured region, adjacent uninjured muscle, and posterior epicardium, respectively. Size of plus signs corresponds to relative magnitudes of positive potentials registered at different sites within injured region. Electrodes are located as in Fig. 2: over anterior wall (*A*), over anterolateral wall (*AL*), in cavity (*C*), and over posterior wall (*P*). Broken lines indicate angles subtended by electrodes with epicardial or endocardial surface of injury.

Injured region presents positive potential during electrical systole which decreases in magnitude from epicardium to endocardium and from center to margins. Uninjured epicardial and intramural muscle adjacent to injury is isoelectric while epicardium of posterior wall opposite injury is negative. Electrodes *A* and *AL* subtend angles with injured epicardium and therefore register the positive epicardial potential. Elevated S-T segments thus occur in leads *A* and *AL*. Since electrode *A* subtends a wider angle than electrode *AL*, it records more marked S-T segment elevation. Electrode in cavity subtends wide angle with injured endocardium but records only slight S-T segment elevation because the positive endocardial potential is of relatively low magnitude. Electrode *P* faces the posterior epicardium which presents a negative potential and therefore registers depressed S-T segments. The negative potential recorded opposite the injured region appears to represent a reciprocal effect and may be related to a vector drawn through the injury toward the point of maximum positivity. Since such a vector would be directed from endocardium to epicardium of the injured wall, as in subepicardial injury, it would point away from the negative zone over the opposite wall.

recorded in the experiments. Since the uninjured epicardium over subendocardial extensions of the injury is isoelectric, the only potential on the anterior surface is the positivity over the transmural portion of the injury. An electrode at any site on the precordium over the anterior or anterolateral wall thus registers either elevated or isoelectric S-T segments, depending on the angle which it subtends with the injured epicardial area. Electrode *A*, directly over the injury, subtends a wide angle with the injured epicardial area and therefore registers marked S-T segment elevation. Electrode *AL* over the anterolateral wall subtends a smaller angle with the injured epicardial area; hence it registers elevated S-T segments of lower amplitude than those in the anterior lead. As compared with the epicardial surface, the endocardium of the anterior wall presents more extensive injury. The magnitude of the positive injury potential at the endo-

cardium, however, is many times less than at the epicardium. An electrode in the cavity thus records only slight positivity although it subtends a wide angle with the injured endocardial area.

The injured region represented in Fig. 9 is progressively wider from epicardium to endocardium but is progressively more positive from endocardium to epicardium. Hence the injury may be described as primarily subendocardial with respect to extent and primarily subepicardial with respect to its electrical effects. A vector might therefore be drawn, as in subepicardial injury, through the center of the ventricle toward the surface of the injured region. Since the vector would point away from the posterior surface opposite the injury, it may be related to the occurrence of depressed S-T segments over the posterior wall. The S-T segment displacement in the limb leads likewise would be typical of subepicardial injury in the anterior wall, consisting of elevation in Lead I and depression in Leads III and aV_F. This hypothesis thus appears to account both for the reciprocal relationship between anterior and posterior precordial leads and for the limb lead changes commonly seen in patients during the early stage of anterior infarction.

In a previous study the observation was made that chronic subendocardial infarcts produced by coronary artery ligation do not affect direct epicardial and precordial leads.[2a,b] The present study suggests that this is also true of subendocardial injuries resulting from coronary disease. As shown in Table I and Figs. 3 and 4, the amount of S-T segment elevation recorded from subendocardial levels of injured regions is much less than that recorded from superficial levels. Injured subendocardial muscle thus appears to give rise to relatively slight injury effects. Moreover, the uninjured epicardium over subendocardial extensions of transmural injuries was found to yield isoelectric S-T segments (Fig. 7). These observations are difficult to reconcile with the prevailing opinion that subendocardial injury may cause S-T segment depression in precordial leads. Since direct leads from within injured subendocardial muscle showed only slight injury effects while direct leads from overlying uninjured epicardium remained normal, it seems improbable that leads from the relatively remote precordium could be affected by subendocardial injuries.

By assuming that the electrical effects of injury in human hearts are comparable to those in dog hearts, the preceding comments may be applied to clinical electrocardiograms from patients with angina pectoris. These patients may show S-T segment depression of as much as 6 to 10 mm. in several precordial leads during anginal attacks or after exercise, presumably owing to subendocardial anoxia. During the present experiments, however, injuries produced by anoxia yielded S-T segment elevation of only 1 to 2 mm. in direct subendocardial leads. The local electrical effects of subendocardial anoxia thus were found to be several times weaker than the electrical effects of angina registered on the precordium. This discrepancy is contrary to Poisson's Law[6,16] according to which the magnitude of a potential varies inversely with the distance from its source. Hence it appears unlikely that the marked S-T segment depression associated with angina may result from subendocardial anoxia as is commonly supposed. If these considerations apply to human hearts, involvement of the outer ventricular layers

rather than the inner layers may be responsible for S-T segment depression in the clinical electrocardiogram.

It is suggested that S-T segment depression may occur in either of two circumstances:

1. Depression of the S-T segment may be observed at the site of an electrode situated over normal muscle opposite to an area of marked S-T segment elevation. This is the well-known reciprocal effect, which has already been discussed in this paper. The circled complex in Fig. 6 is an example of this type of depression.

2. Preliminary investigations now in progress indicate that functional changes at the superficial levels of the ventricular wall directly under the electrode may also cause S-T segment depression (17 experiments). Unless the temperature and humidity at the exposed surface of the heart were kept as normal as possible, these S-T segment changes were not as readily observed. After several methods were tried, the most efficient procedure for this purpose was found to be the use of an incubator of the type used for premature infants. After the heart was exposed, the entire animal was placed in the incubator in which the temperature and humidity were easily controlled. Several hours after the coronary artery had been tied, S-T segment depression often occurred in various areas at the periphery of the infarcted region. This type of depression also occurred, on occasion, after an additional area of injury was produced by a new coronary artery occlusion adjacent to and superimposed upon a previous infarction.

The following preliminary observations have been made with reference to S-T segment depression occurring near the periphery of injured areas.

1. There was no apparent constant relationship of S-T segment depression to the injured area. The depression generally occurred near the periphery of the injured region in large or small patches or islands. Other peripheral areas of a similar appearance showed isoelectric S-T segments.

2. In surface exploration there was no reciprocal relationship between the degree of S-T segment depression and the degree of S-T segment elevation. The S-T segment depression did not occur when the elevation was at its maximum; it was observed when the elevation was waning.

3. S-T segment depression was evanescent, appearing and disappearing in minutes or seconds. The S-T segment elevation, on the other hand, was always more stable and presented a fairly constant pattern of progression and recession.

4. Further information concerning this problem was obtained by simultaneously recording subendocardial leads with leads from the overlying epicardium. It was found that there was no relationship between the S-T segment deviation of these two sites. The S-T segment of the subendocardial lead was either isoelectric or slightly elevated and remained constant whether the overlying epicardial lead showed marked, moderate, or no S-T segment depression. This may be considered evidence that the current theory that S-T depression observed clinically is due to subendocardial ischemia may not be valid. This experiment suggests that this type of S-T segment depression is due to local functional changes, related in some unknown manner to ischemia, occurring at the ventricular surface. The nature of the functional changes causing the S-T

segment depression is unknown, but the S-T segment depression is apparently not a direct result of subendocardial ischemia.

5. It was not possible to predict from the appearance of the surface of the heart whether or not S-T segment depression would be recorded. Depressed S-T segments have been recorded over normal-appearing muscle, over cyanotic but contracting muscle, and from cyanotic but ballooning or noncontractile muscle. S-T segment depression has been recorded from surface areas showing normal QRS complexes and from surface areas showing mural QS complexes.

These observations suggest that functional changes in the superficial layers of the myocardium may be responsible for the S-T segment depression associated with such conditions as angina pectoris. Such functional changes at superficial levels of the ventricle also may account for the depressed S-T segments occurring in some clinical cases of acute coronary artery occlusion. Frequently after occlusion there may be S-T segment elevation in two or three precordial leads and S-T depression in immediately adjacent leads. In these instances it is obvious that the S-T deviations cannot be of the "reciprocal" type.

Another clinical instance in which S-T segment depression sometimes occurs is after massive subendocardial infarction. This has been ascribed by some to ischemia of the subendocardial region. However, in view of the above observations it is postulated that functional changes in the normal appearing superficial layers may be the cause of this S-T segment depression. It might be expected that with such marked anatomic and functional changes in the subendocardial region that some functional changes would also be present in the epicardial layers of the heart. It is postulated that it is the epicardial change that causes the S-T segment depression.

QRS-Wave Changes.—Associated with the S-T segment elevation recorded from injured regions were changes in both the positive and negative components of the QRS complex. Leads from the outer layers of the injury showed a gradual increase in amplitude of the R wave and decrease in amplitude of the S wave after coronary artery ligation. The QS waves registered at deeper levels of the injury also decreased gradually in amplitude. These QRS changes resembled the S-T segment displacement in two respects: they were entirely in an upward direction, and they decreased progressively from epicardium to cavity. Thus the Rs waves in control leads from the outer few millimeters of the ventricle rose markedly to form tall, monophasic deflections merging with the elevated S-T segment; the intramural rS waves recorded above midventricular levels became predominantly positive while those registered from deeper levels became less negative; and the QS waves in subendocardial and cavity leads decreased slightly in depth (Fig. 3). The electrical effects of injury recorded during the present experiments may therefore be summarized as an increase in positivity beginning with the QRS complex, including the S-T segment, and diminishing progressively from epicardium to endocardium of the injured region. No electrical changes were observed outside the injured region during the first thirty minutes of observation, except in the underlying cavity which yielded slightly elevated S-T segments and on the surface of the opposite wall where slight to moderate S-T

segment depression was recorded. S-T segment depression and T-wave abnormalities will be discussed more fully in subsequent communications.

The R-wave changes seen in the present study appear to conflict with the theory that injured muscle undergoes a subnormal change in the intensity of polarization. If injured regions either polarized or depolarized incompletely, the voltages produced by depolarization would be abnormally small. Hence the R waves recorded over such regions should be reduced in amplitude. Similarly, a delay in rate of depolarization should reduce the height of the R wave as the total voltage would remain constant but would develop over a longer period. The R wave thus would ascend more gradually to a later but lower peak. During the present experiments, however, the peak of the R wave in epicardial and subepicardial leads from injured regions was both higher and later than in control tracings. According to the membrane theory, these changes suggest a supernormal rather than a subnormal change in the intensity of polarization. A similar phenomenon was observed in uninjured ventricles with bundle branch block which yielded abnormally tall, wide R waves at all levels from epicardium to cavity as a result of abnormal mural depolarization.[3]

SUMMARY AND CONCLUSIONS

1. Previous theories and experimental observations concerning the electrocardiographic changes associated with cardiac injury are reviewed. The theoretical explanation of S-T segment displacement resulting from coronary artery occlusion has been a controversial subject. Experimental study previously consisted of recording epicardial, cavity, and limb leads after the production of injuries by direct trauma or by coronary artery ligation. The present investigation was designed to obtain additional information by means of intramural leads.

2. In each of sixteen animals, epicardial leads from the anterior wall of the left ventricle were registered simultaneously with subepicardial, midmural, subendocardial, and cavity leads from directly underlying sites. Insertion of the intramural electrodes elicited marked S-T segment elevation in the subepicardial leads, less pronounced S-T segment elevation in midmural leads, and minimal S-T segment elevation in subendocardial leads. After these electrode-induced injury effects subsided, the left anterior descending branch of the coronary artery was ligated to produce injury in the region containing the electrodes.

3. Discoloration and ballooning of limited areas on the epicardial surface of the anterior wall developed several seconds after coronary artery ligation, delineating transmural portions of the injury. Epicardial leads from these areas showed S-T segment elevation beginning within 30 to 60 seconds after ligation and reaching a maximum in 5 to 7 minutes. The amount of S-T segment elevation was greatest in leads from the center of the injured area and decreased as the electrode was moved toward the margins. Isoelectric S-T segments were recorded from all sites on the epicardial surface of the anterior wall outside the margins of the injured area. Depressed S-T segments occurred in leads from the surface of the posterior wall.

4. Intramural and cavity leads recorded directly beneath the injured epicardial area presented S-T segment elevation. The amplitude of the S-T segment in simultaneously recorded tracings diminished from epicardium to cavity; that is, the elevation was greatest in epicardial leads, somewhat less in subepicardial, considerably less in midmural, relatively slight in subendocardial, and minimal in cavity leads.

5. Control tracings from the epicardium and outer ventricular layers presented RS waves while those from the inner layers and cavity showed pure QS waves. After coronary artery ligation, tracings from the injured region exhibited a gradual decrease in depth of the S or QS wave while the upstroke of the R wave became progressively taller but did not change in slope. These QRS changes, like the S-T segment changes, decreased in magnitude from epicardium to cavity.

6. Subendocardial and midmural leads were recorded directly beneath normal-appearing epicardium adjacent to the injured epicardial area in eight instances. Elevated S-T segments appeared in the intramural tracings, establishing the presence of subendocardial injury. Tracings from the overlying epicardium presented isoelectric S-T segments.

7. Simultaneous intramural leads were recorded at 2 to 3 mm.-intervals along a line extending laterally from the center of the injured region in two animals. The S-T segment decreased in amplitude at progressively greater distances from the center of injury, becoming isoelectric in leads recorded beneath normal-appearing epicardium several millimeters beyond the injured epicardial area. This and the preceding observation indicate that injuries produced by coronary artery ligation are broader intramurally than at the epicardium.

8. In no instance during the first thirty minutes of observation were depressed S-T segments recorded from uninjured epicardial or intramural muscle adjacent to the lateral boundaries of the injured region. Depressed S-T segments also failed to occur in cavity leads and in subendocardial leads recorded within ½ mm. of the cavity directly beneath injured epicardial areas. These findings conflict with two frequently advanced hypotheses which relate S-T segment displacement to a dipole at the boundary between injured and uninjured muscle.

9. A new hypothesis is suggested to account for the elevation of the S-T segment in clinical electrocardiograms recorded during the early stages of infarction.

10. Depressed S-T segments were observed experimentally under the following circumstances: (a) When, under conditions of temperature and humidity approaching the normal, the injury was allowed to persist for several hours; (b) When an acute injury was superimposed upon a previously established infarct. Under these circumstances, simultaneous electrocardiograms of subendocardial and overlying epicardial surface leads were taken. It was found that there was no relationship between the two electrocardiograms, the subendocardial lead remaining constant while in the surface lead the S-T segment level fluctuated between markedly depressed and normal. It is therefore suggested that this type of depression may be due to functional changes in the outer layer of the ventricular wall, and not to subendocardial ischemia.

11. There would appear to be two types of S-T segment depression: (a) the well-known reciprocal type occurring over normal muscle opposite the area of S-T segment elevation produced by acute injury, and (b) depression occurring as a result of functional changes, of an unknown nature, at the myocardial surface.

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MECHANISM OF THE HEPATOJUGULAR REFLUX TEST IN CONGESTIVE HEART FAILURE

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IT IS well known that pressure exerted by placing both the observer's hands upon the abdominal wall over the region of the liver results in an increase in systemic venous pressure in a subject with congestive heart failure.[1-5] This response is known as the hepatojugular reflux. The degree of elevation in venous pressure varies, being most pronounced when venous hypertension exists but also occurring in the presence of a normal level of venous pressure in an abnormal subject.[6] A normal person with normal venous pressure will experience only slight, if any, elevation in venous pressure: In many instances his venous pressure will decline.

The hepatojugular reflux is of clinical as well as physiologic importance. The response of venous pressure to pressure over the liver is employed clinically as a diagnostic test in congestive heart failure as well as other cardiac states which are accompanied by generalized venous hypertension, for example, concretio cordis and pericardial effusion. The response is not pathognomonic of congestive heart failure but is useful in the diagnosis of cardiac insufficiency under certain clinical circumstances in which the state of myocardial function requires clarification. When employed properly, therefore, the hepatojugular reflux is of value in cardiology.

The mechanism for the elevation in venous pressure in association with certain disturbances in the cardiovascular system and for failure of venous pressure to rise in the normal subject is puzzling. This intriguing phenomenon has been the subject of considerable thought and speculation, especially by those who have observed it. These well-known observations need not be repeated here, since they add nothing to this discussion and since the existence of a hepatojugular reflux has been confirmed by all who have measured venous pressures before and during the application of pressure over the hepatic region. It is the purpose of this note to present certain concepts which offer a plausible explanation for this response which has been observed repeatedly and reported previously.[4]

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THEORETIC CONSIDERATIONS

For purposes of orientation and for expediency in presenting ideas of the possible mechanism of the hepatojugular reflux, certain previously presented physiologic concepts considered to exist for chronic congestive heart failure will be reviewed. It has been noted previously that in congestive heart failure the venous pressure is elevated primarily because venous tone is high.[5,6] Evidence for the increase in venous tone in congestive heart failure is available elsewhere[5-7] and will not be reviewed here.

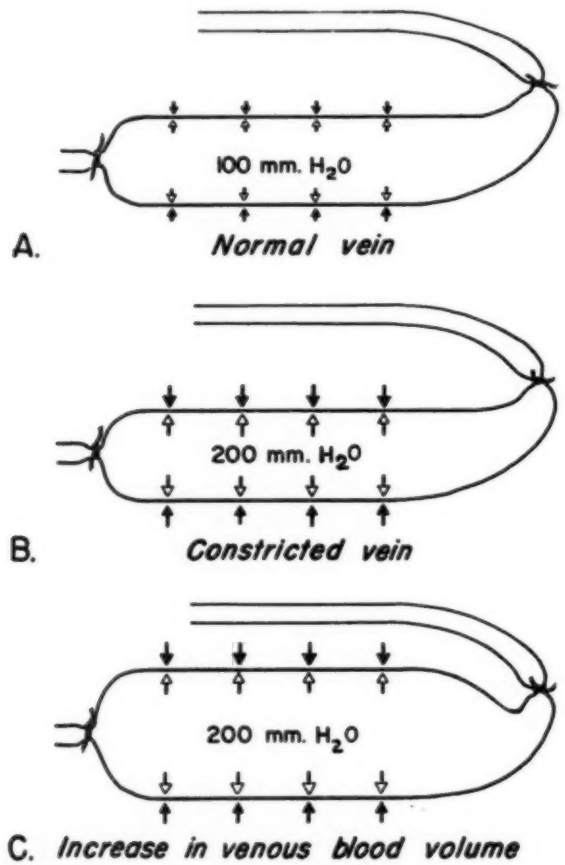

Fig. 1.—Mechanisms of venous hypertension. Diagrammatic representation of the influence of venous tone and of blood volume upon venous pressure in a segment of vein. *A*, A segment of vein of given blood volume and venous tone with a venous pressure of 100 mm. H_2O. *B*, The same segment of vein shown in *A* with venous tone increased. Because the blood is incompressible, the tone of venous wall may increase, squeeze more tightly upon the blood within, and increase the venous pressure without any associated change in volume of the venous lumen. Thus, venoconstriction may be only "venotightening" and not necessarily "venonarrowing" or decrease in volume of the lumen of the veins. With vasoconstriction there may be only a more intense squeezing upon the blood within by the surrounding wall. *C*, With an increase in the volume of blood within the vein, the venous pressure is increased as the wall of the vein becomes stretched and offers resistance to distention. This is a second cause for an increase in venous pressure.

It has previously been indicated that venous hypertension is generalized and symmetric in all systemic veins and that venous pressure can increase only by either or both of two mechanisms[5,6]: (1) increase in venous tone, or the tightness with which the walls of the veins constrict upon the blood within, and (2) increase in volume of blood within the veins, i.e., a larger volume of blood "packed" more tightly within the veins (Fig. 1).

Blood volume may increase, remain unchanged, or actually decrease in chronic congestive heart failure. It is surprising to most clinicians that blood volume may change little, since the distended neck veins of patients with failure are often erroneously considered as evidence of an increase in blood volume. Careful consideration of the evidence indicates that blood volume is not necessarily altered.[5,6] The most reasonable explanations for the distended neck veins will be presented in the following paragraphs.

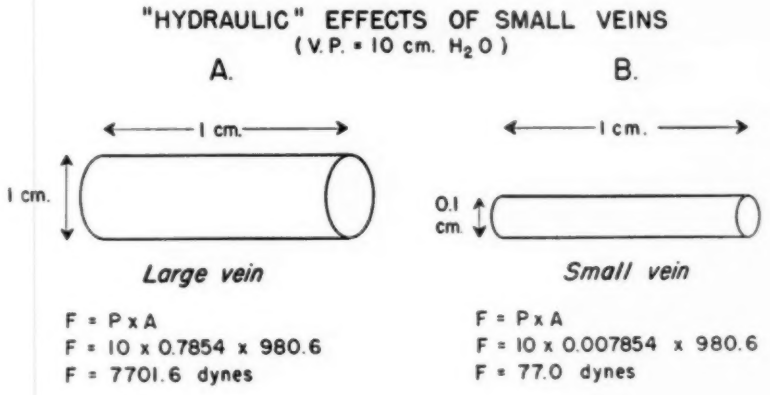

Fig. 2.—Diagrammatic illustration of the relative forces acting per unit length of large and small vein for the same pressure. The smaller the diameter of the vein, the less the force acting on a unit length of vessel. A unit length of small veins may contract with a greater advantage than a unit length of large vein because of the relatively small force it has to overcome. This is similar to the principle in hydraulics, exemplified by the well-known hydraulic jack. Because of the relatively small force involved, blood can readily be shifted from peripheral veins to the large central ones. There is a need to evaluate the influence of levers in vessels of both sizes; the larger one would have an advantage from that point of view. The tension per muscle fiber or contracting molecular unit remains to be determined, as well as the degree of tension developed per contracting unit per unit of intensity of sympathetic impulse for large and small vessels. Such factors are important for a more thorough understanding of venous tone of the entire venous system.

That *venous pressure* is elevated in congestive failure is indisputable. If this elevation is not due to an increase in blood volume, it must be due to an increase in *venous tone*, i.e., the veins must "squeeze" more tightly upon the blood contained therein. Further evidence in support of this concept has been presented previously.[5-7] The blood which distends the veins of the neck of patients with failure has probably been shifted into them from the smaller veins and other vessels of the periphery due to the generalized increase in venous tone. Only a small quantity, if any, of the blood shifted into the larger central veins could conceivably originate from the arterial system, since arterial blood pressure

remains unchanged and the total volume of blood in the systemic arteries is only about 500 c.c. In fact, if the venous system were behaving normally, it could accommodate the addition of this entire volume with no change in venous pressure, a fact so well demonstrated daily in hospitals by transfusion procedures.

That venous hypertension in chronic congestive heart failure is not due to a "dam in the stream" or passive congestion has been discussed in detail elsewhere.[5,6] From these discussions it became evident that the venous pressure is elevated in congestive failure primarily because of a generalized increase in *venous tone*, i.e., because the veins squeeze more tightly upon the blood within.

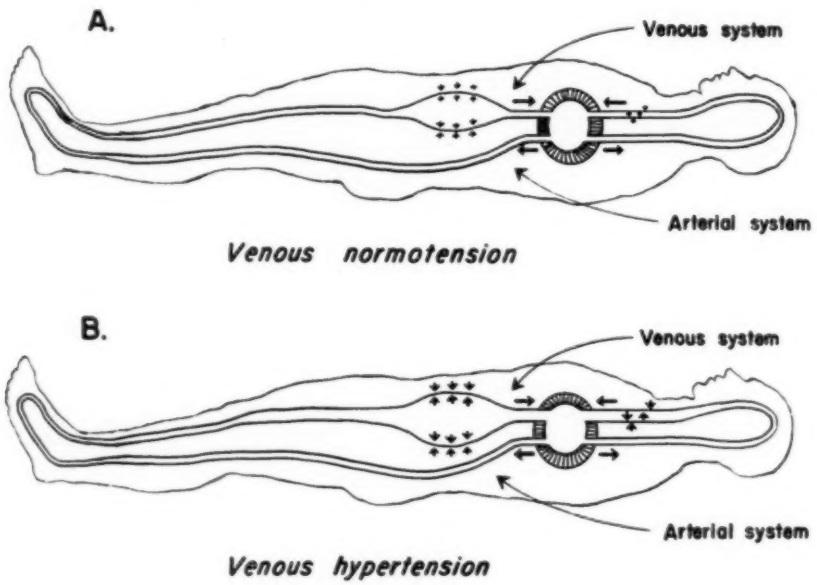

Fig. 3.—Diagrammatic representation of the distribution in venous pressure and venous blood volume in a subject (*A*) with normal venous pressure and in a subject (*B*) with venous hypertension. Consult the text for details.

And if the tension of the smooth muscle in the walls of all veins, regardless of size, is increased equally, then blood would be forced from the smaller ones into the larger ones (Fig. 2). This is a well-known principle employed in engineering, for example, the hydraulic jack. This, of course, would be true if each unit length of vein contained the same number of contracting muscle units and each muscle unit increased in tension equally. Factors such as these require further careful study for elucidation of the relation of hemodynamic phenomena to vascular function.

EFFECT OF PRESSURE OVER THE HEPATIC REGION OF THE ABDOMEN UPON VENOUS PRESSURE

Normal Subject.—No elevation in venous pressure is observed when pressure is applied to the hepatic region of the abdomen of the normal subject, in whom the regulating mechanisms and measurements of venous pressure are normal.

Nor would a rise be expected, for if blood were squeezed out of the liver or splanchnic vessels into other veins, these veins would accommodate this added amount of displaced blood by increasing in volume while simultaneously maintaining the same tone or "tightness of fit" or "squeeze" upon the blood within (Fig. 3). One of the functions of the venous system is to maintain a normal venous pressure in spite of the introduction of such factors as local application of pressure externally or an increase in blood volume within. This is what happens when a normal person receives a transfusion of 500 to 1,000 c.c. of blood without experiencing a rise in venous pressure. The compensatory relaxation in venous tone is further illustrated by the fairly frequent decline in venous pressure accompanying pressure over the hepatic region. This is evidence of overcompensatory relaxation or decrease in tone or tightness of fit of the veins.

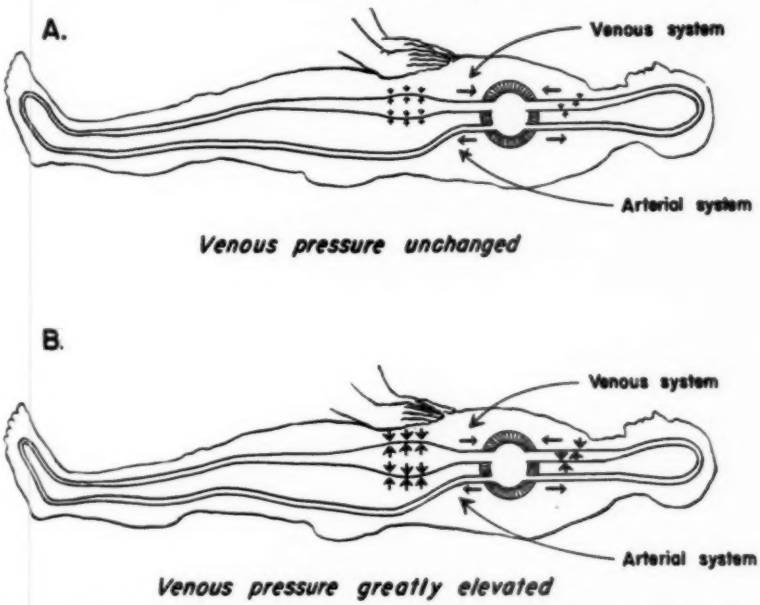

Fig. 4.—The influence of manual pressure over the hepatic region in the same two subjects illustrated in Fig. 3. Consult the text for details.

Therefore, a venous system with normal pressure whose walls are not rigidly fixed either for tight fitting or increased tone but rather are able to distend or relax to maintain a normal pressure within will not exhibit a rise in venous pressure when external pressure is applied to it. In brief, the veins are functioning normally. They are set for neither high nor low tone but at the proper tone to maintain normal venous pressure with the necessary readjustments available to meet the needs of the moment.

Chronic Congestive Heart Failure.—With chronic congestive heart failure the venous system or the tension of the smooth muscles of the media is adjusted physiologically for high tone, to maintain a tight fit around the blood or to squeeze tightly upon the enclosed blood. When pressure is applied externally over such a large area of the venous system, such as the hepatic and splanchnic areas, and

blood tends to be displaced, the other segments do not distend readily but rather tend to squeeze more tightly upon the blood within. Lost is the normal venous function of distending or constricting to accommodate a change in volume while simultaneously maintaining the same tightness of fit upon the blood within and, in turn, the same venous pressure (Fig. 4). Venous function is altered; it is adjusted to maintain a new physiologic state of high venous tone and high venous pressure. There must be a functional active increase in venous tone due to greater tonal contraction or tightening of the smooth muscle of the wall of the veins. This "tight" venous system must be a physiologic state associated with the many well-known clinical states manifesting generalized or regional venous hypertension.

In a patient with congestive heart failure, the volume of blood that may be displaced as a result of pressure over the hepatic area may be immeasurably small. It is probably much less than that transferred in the normal subject but, when displaced within a tight venous system, it results in a definite elevation of venous pressure.

By the same reasoning, it is evident that the pressure in any segment of the venous system of a patient with congestive failure and venous hypertension will further increase if the veins are pressed or squeezed upon. For example, it is well known that contractions of the skeletal muscles of an arm or leg will increase the pressure within the large veins of the part to a greater degree in the subject with congestive failure than in the normal one. This effect is produced by the muscles squeezing upon the members of veins contained in the tight venous system. A given amount of exercise will likewise increase venous pressure in the patient with congestive failure to a greater degree than in the normal subject. Such a response to exercise would occur in any physiologic state associated with venous hypertension, as noted in the following discussion. The same mechanisms would apply to the increase in venous pressure associated with deep inspiration, in which the diaphragm increases intra-abdominal pressure and, consequently, squeezes upon the veins within the abdomen.

Venous Hypertensive States.—From the foregoing discussion, it becomes evident that venous pressure will rise with pressure over the hepatic area in any physiologic state, normal or abnormal, in which venous tone is high and the normal regulating mechanisms for venous pressure are sluggish or altered in such a way that the system cannot adjust to changes in volume generally or locally while maintaining a constant venous tone. Thus, venous pressure would be expected to rise in the presence of cardiac tamponade, regardless of the cause, or in association with physiologic states in which blood volume is high and the venous system is overdistended. It would be interesting to study the relationship of changes in volume to the maintenance of venous pressure throughout the venous system in intact man. There must be critical increases and decreases beyond which the tone of the venous system adjusts poorly to external pressure or further changes in blood volume.

It becomes evident that any procedure which reduces venous tone, i.e., causes the veins to squeeze less tightly upon the blood within and which also

allows for segments of the venous reservoir to distend and accommodate additional blood displaced therein, will tend to return the hepatojugular reflux to normal. Thus, a vasodilating agent would be expected to return the response toward normal in subjects who have generalized venous hypertension.

Experiments of this type were performed by administering hexamethonium bromide, 5 to 25 mg., intravenously to subjects with chronic congestive heart failure. Results of a few of these observations are presented in Table I and Fig. 5. Venous pressure was measured in the median basilic vein with proper correction for heart level and recorded as the control level of venous pressure.

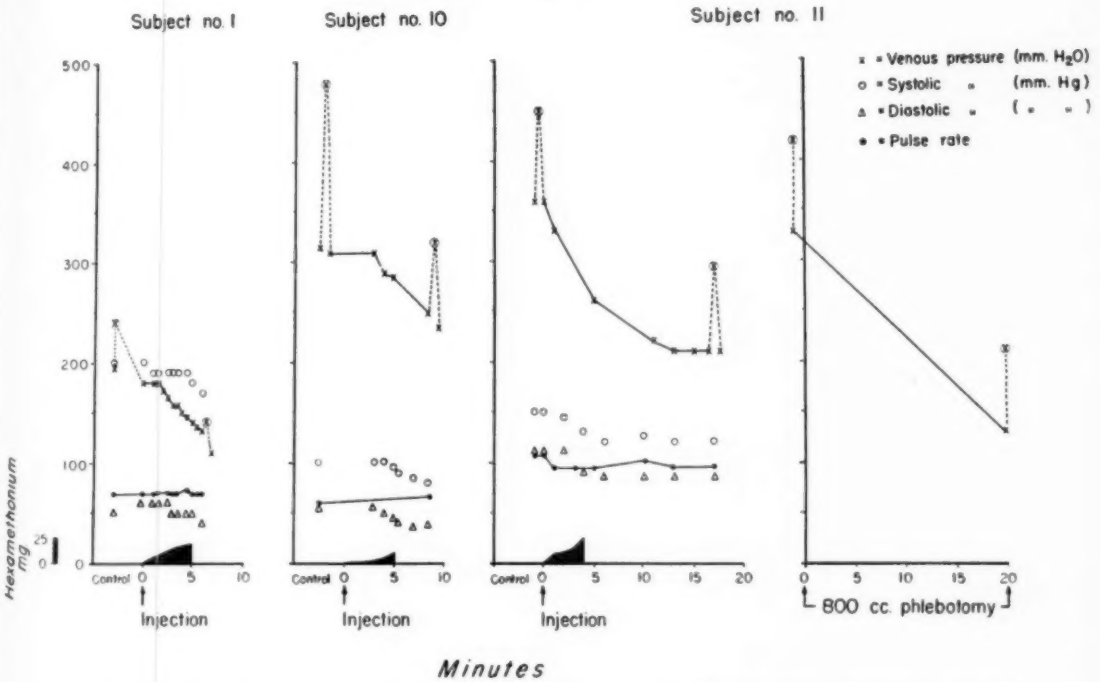

Fig. 5.—These graphs summarize four types of response of arterial and venous pressures and pulse rate to intravenous injection of hexamethonium observed in the studies. The dotted lines at the beginning and at the end of each curve represent the response of venous pressure to pressure over the hepatic area. See text for details.

Then, with the subject relaxed, pressure was exerted over the liver for one minute, during which time the change in level of venous pressure was recorded. These same measurements were obtained after the injection of the hexamethonium. An attempt was made to exert the same amount of pressure over the same area each time this maneuver was performed, but this, admittedly, was not standardized.

The control venous pressure was abnormally elevated in all subjects. There was a uniform decline in venous pressure following administration of the hexamethonium, the mean being 225 mm. of water, returning to normal in only two patients.

TABLE I. INFLUENCE OF HEXAMETHONIUM AND PRESSURE OVER THE LIVER ON VENOUS PRESSURE IN 12 PATIENTS WITH CONGESTIVE HEART FAILURE

SUBJECT	DOSE (MG.)	INJECTION TIME (MIN.)	VENOUS PRESSURE (mm. H_2^0)				ARTERIAL PRESSURE (mm. Hg)		PULSE RATE CHANGE POST-INJECTION	CLINICAL STATE
			PREINJECTION		POSTINJECTION		PRE-INJECTION	POST-INJECTION		
			CONTROL	PRESSURE OVER LIVER	CONTROL	PRESSURE OVER LIVER				
1.	25	5	194	240	132	142	200/50	170/40	N.C.* 68	C.F. HASHD**, LVH*** 3+, CHF§ On digitalis and mercurials
2.	25	9	278	358	240	280	145/90	125/80	95–88	C.M. 59 yr. HCVD§§, CHF
3.	12.5	8	438	>600	280	400	140/100	90/70	120–108	C.F. 33 yr. CHF. On digitalis and mercurials
4.	7.5		315	435	223	318	144/114	138/100	64–68	43 yr. HCVD with CHF
5.	25	8.5	414	486	300	400	190/110	146/86	N.C.	HHD† with CHF On digitalis, mercury, low-salt diet, hexamethonium, 6 doses, 250 mg.
6.	25	5	282	——	255	——	170/110	140/80	100–88	HASHD, CHF 4+, fibrillation On digitalis and mercurials
7.	25	≈10	340	415	270	310	130/80	94/60 86/40 10 min. later	N.C.	ASHD‡, auricular fibrillation

8. 10/7/52	25	≈10	294	370	208	254	140/90	118/84		HASHD, CHF
10/10/52	25	4	256	340	176	230	140/92	116/74		On digitalis and mercury, with considerable improvement before first test
9.	12.5	8	356	425	280	355	110/70	80/50	N.C. 80	40 yr. RHD#, auricular fibrillation, CHF On digitalis and diuretics
10.	10	5.5	263	343	135	220	110/78	80/50	80–70	RHD, severe CHF, mitral stenosis, auricular fibrillation
11.	10	5	315	480	250	320	100/56	80/38	60–66	35 yr. Interauricular defect, severe CHF, auricular fibrillation On digitalis and diuretics
12.	12.5	4	360	450	210	295	150/110	120/85	107–95	44 yr. HCVD, severe CHF On digitalis and diuretics
After phlebotomy	800 c.c. in ? time		330	420	130	210				
Mean			327	419	225	293				

*No change
**Hypertensive arteriosclerotic heart disease
***Left ventricular hypertrophy
§Congestive heart failure
§§Hypertensive cardiovascular disease
†Hypertensive heart disease
‡Arteriosclerotic heart disease
#Rheumatic heart disease

Compression over the liver resulted in an increase in venous pressure of 46 to 165 (mean 92) mm. of water before administration of the hexamethonium and 10 to 120 (mean 68) mm. of water following the injection. Variation in relaxation of the subject and the degree of pressure exerted over the liver were probably important factors contributing to the wider variation in these pressure changes. The rise in venous pressure on compression over the liver was slightly greater after injection of the hexamethonium than the control response in two subjects. In Subject 8 the observations were repeated, the same magnitude and direction of response being obtained. Phlebotomy with removal of 800 c.c. of blood from Subject 12 produced the same type of response as resulted from the intravenous administration of the hexamethonium. The responses in venous pressure shown in Table I and Fig. 5 support the existence of increased venous tone or "tightness" of the venous system in these subjects with chronic congestive heart failure.

It is interesting to note that in all instances the external jugular veins of these patients, who were semirecumbent (30-45°), collapsed as the venous pressure declined during administration of the hexamethonium. In every instance there was improvement in breathing, and the sensation of suffocation was greatly diminished or disappeared. In several of the patients this improvement progressed to compensation in association with a definite diuresis.

SUMMARY

Certain theoretic concepts are presented for the elevation in systemic venous pressure produced by manual pressure over the hepatic region in subjects with chronic congestive heart failure. This response, known as the hepatojugular reflux, is to be expected in any person with generalized systemic hypertension and constitutes further evidence that venous tone is increased in patients with fongestive failure. Experiments on subjects with chronic congestive heart cailure supported the existence of a generalized increase in venous tone in congestive failure.

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AURICULAR FLUTTER ASSOCIATED WITH COMPLETE HEART BLOCK

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INTRODUCTION

THE association of complete atrioventricular block and auricular flutter is rare. Seventy-one previous cases have been reported, plus one additional case included in this paper. In each of these patients, complete atrioventricular dissociation accompanied by auricular flutter has been demonstrated by electrocardiographic study. The first report of this cardiac abnormality was by Jolly and Ritchie[31] in 1910. Tabulation of the larger series of documented cases gives evidence of the relative rarity of this condition (Table I). Isolated instances are included in the bibliography.

TABLE I

AUTHOR	SURVEY (ELECTROCARDIOGRAMS)	INCIDENCE (NO. CASES)
White[27]	10,000	None, although there were 104 isolated instances of atrial flutter and 79 cases of complete heart block
Willius[28]	40,000	An incidence of 1 case in 158 cases of auricular flutter
Smith and Smith[21]	25,000	3
Di Gregorio and Crawford[7]	20,000	2
McMillan[8] and Bellet[3]	16,000	1
Brandman, et al.[19]	12,948	5
Thorberg[10]	No data available	3
Hanssen[17]	59,000	7

The seventy-one cases mentioned here are included in the bibliography as References 1 through 26.* The foreign literature has also been surveyed, and a summary of all seventy-one cases is included in the discussion. Our own case is presented with clinical data, serial electrocardiograms, phonocardiogram, and pertinent chest x-rays.

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*The reference to 29 of the 71 cases is completely reviewed in the AM. HEART J. in 1937 by Jourdonais and Mosenthal.[4]

CASE REPORT

E. M., a 63-year-old white male was admitted to the Veterans Administration Hospital, Madison, Wis. on April 8, 1953, for treatment of pulmonary tuberculosis, the diagnosis having been established in February, 1953. At the time of hospital admission here, the patient was essentially asymptomatic, although he had noted a slight increase in his productive cough within the past several months. He denied shortness of breath or exertional dyspnea, and at no time had he been aware of chest pain or ankle edema. Systemic review did not prove pertinent. Past medical history revealed that he had undergone an exploratory laparotomy in 1948 because of a perforated peptic ulcer. A right inguinal herniorrhaphy was performed in 1949. The social and family histories were not contributory.

Review of previous hospital admissions elsewhere showed that when he was hospitalized in 1949, his electrocardiogram (ECG) disclosed a right-axis pattern with inversion of the T waves in Lead I, CF_2 and CF_4. The diagnosis at that time was "coronary heart disease with myocardial damage." A subsequent ECG taken one month later showed a similar pattern, and once again it was felt that the changes were on the basis of coronary insufficiency. A routine ECG was also taken shortly before hospital transfer here on April 3, 1953, which revealed persistence of the T-wave inversion pattern in the right precordial leads and a borderline P-R interval.

Physical examination: At the time of hospital admission, physical examination revealed a rather thin, elderly white male. Chest expansion was fairly equal bilaterally, although the costal margins moved inward with deep inspiration. There was increased resonance to percussion over the bases bilaterally. Numerous coarse râles and rhonchi were heard over both bases, posteriorly, more marked on the right. The blood pressure was 118/76 mm. Hg, and the radial pulse 80 per minute and regular. The mitral first sound was reduplicated and forceful. The aortic second sound was slightly greater in intensity than the pulmonic second sound. No cardiac murmur was described. A large ventral hernia was easily reducible. There was no evidence of ankle edema, and the dorsalis pedis pulses were readily palpable.

Laboratory: An admission white blood count was 10,900 with a normal differential. Hemoglobin was 14.2 grams. Urinalysis was normal. His sputum was positive for tubercle bacilli on both smear and culture. Routine blood Kahn was positive with subsequent quantitative Kahn of 16 units. A spinal fluid examination yielded a negative Wassermann and gold sol curve.

Chest x-ray on admission showed the cardiovascular silhouette to be within normal limits as to size, although the right-heart border was somewhat prominent. There were extensive healed rib fractures bilaterally. The findings of bilateral minimal pulmonary tuberculosis, with fairly extensive basilar bronchiectasis, moderate pulmonary emphysema and an interstitial type of pulmonary fibrosis were suggested. An orthodiagram done on April 23, 1953, showed the aorta to be moderately dilated and elongated with the heart size at the upper limits of normal as regards the total frontal area and transverse diameter.

Course in hospital: The patient was started on a tuberculosis protocol of absolute bed rest, streptomycin, 1 Gm. twice weekly, and para-amino-salicylic acid, 12 Gm. daily. Isoniazid, 100 mg. thrice daily, was subsequently substituted for the PAS because of gastric upset. He received 8,000,000 units of penicillin for treatment of what was thought to be late latent syphilis, with no subsequent changes in the quantitative Kahn test. On the morning of May 21, 1953, at 5:30 A.M., the patient experienced moderately severe left anterior chest pain with associated shortness of breath, lasting for a matter of minutes. He appeared to be slightly cyanotic and the radial pulse was recorded at 35 per minute. Blood pressure was 128/70 mm. Hg. The heart tones were distant, and no murmur was recorded. A stat ECG (Fig. 1, *A*) revealed a complete heart block with an ischemic T-wave pattern across the entire precordium. The RS-T segment and T-wave changes were not dissimilar to those recorded on previous electrocardiograms with no diagnostic signs of an acute infarct identified. A progress ECG on May 22, 1953, (Fig. 1, *B*) revealed auricular flutter with complete heart block but no change in QRS complexes or T waves. His general condition remained satisfactory, with no appreciable febrile response, leukocytosis, or change in icterus index levels. Several days later he began to experience progressive shortness of breath. A progress ECG (Fig. 1, *C*) on May 28, 1953, showed persistence of the auricular flutter with complete atrioventricular block, with the additive finding of complete left bundle

branch block. A chest roentgenogram taken at this time showed an increase in the bilateral basilar inflammatory disease and bilateral pleural effusion. There was an apparent increase in heart size, although the film was taken at the patient's bedside. This was interpreted as consistent with congestive heart failure.

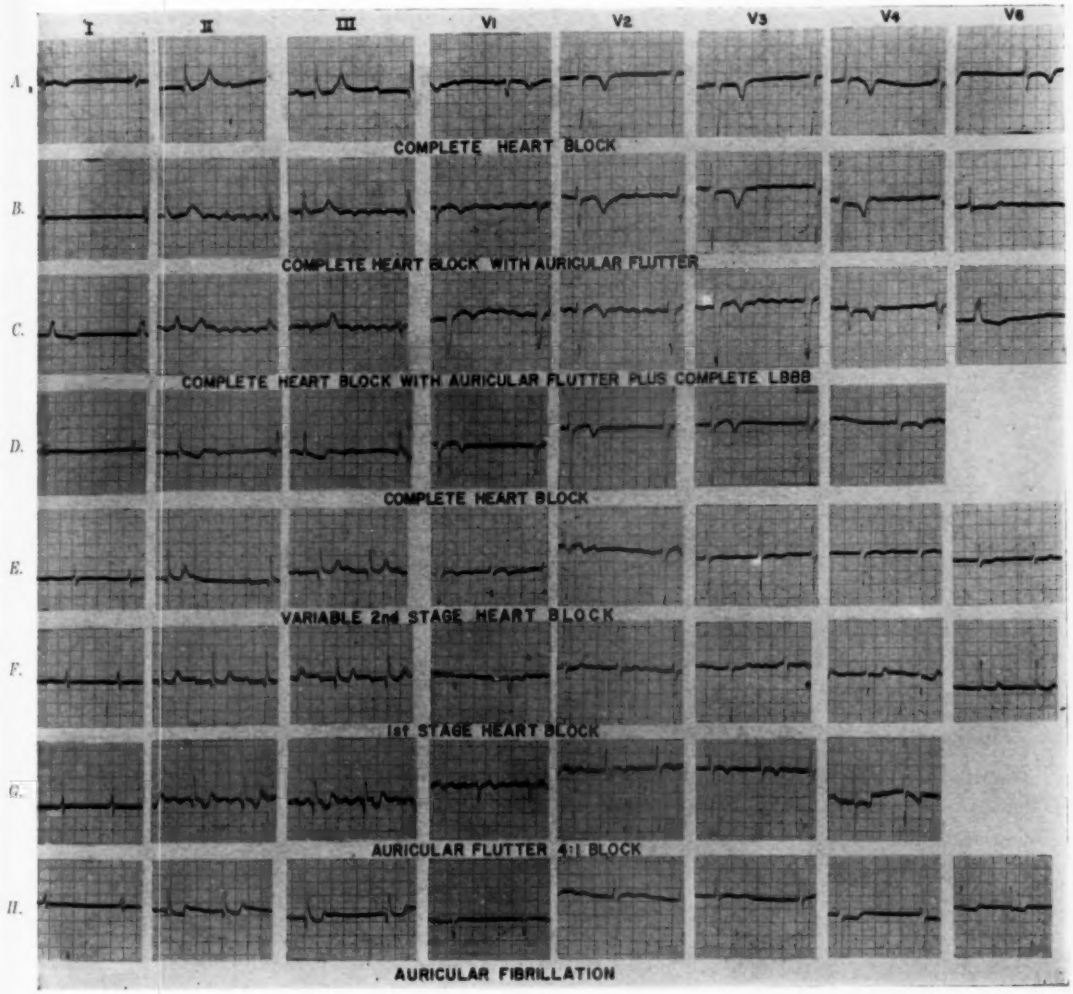

Fig. 1.—Serial electrocardiograms taken from the time of onset of the complete heart block. The patient was followed with frequent tracings and examples are shown of each change in order of progression. *A*, Taken May 21, 1953. *B*, May 22, 1953. *C*, May 28, 1953. *D*, June 1, 1953. *E*, July 28, 1953. *F*, August 5, 1953. *G*, Aug. 20, 1953. *H*, Sept 2, 1953. At the time of this report his pattern is the same as on *H*, Sept. 2, 1953.

Digitalis therapy and a low-salt diet were started on May 28, 1953, utilizing oral digitoxin with digitalization completed by 72 hours. His response was excellent with relief of dyspnea, clearing of the basilar congestion and bilateral effusions. A progress ECG taken on June 1, 1953, (Fig. 1, *D*) revealed persistence of the complete heart block, but the pattern of auricular flutter no longer was evident, nor was the left bundle branch block. A distinct blowing, fairly well-localized systolic murmur of Grade 3 intensity was now heard for the first time over the left lower sternal border in the fourth intercostal space. The mitral first sound was booming in character.

He was given ephedrine, 0.25 mg. orally thrice daily, with no effect. The patient continued to be essentially asymptomatic and was maintained on digitoxin, 0.1 mg. daily. The Grade 3 systolic murmur persisted over the left lower sternal border, and auricular heart sounds were readily audible as rapid clicking sounds over the second right and left intercostal spaces adjacent to the sternum (Fig. 2). There was evidence of minimal cyanosis of lips and fingernail beds. The basic rhythm of complete heart block persisted until July 28, 1953, when a variable second stage atrioventricular block was first noted (Fig. 1, *E*). Subsequently, a first stage block was identified August 5, 1953 (Fig. 1, *F*), with distinct improvement of the ischemic type T waves in the precordial leads.

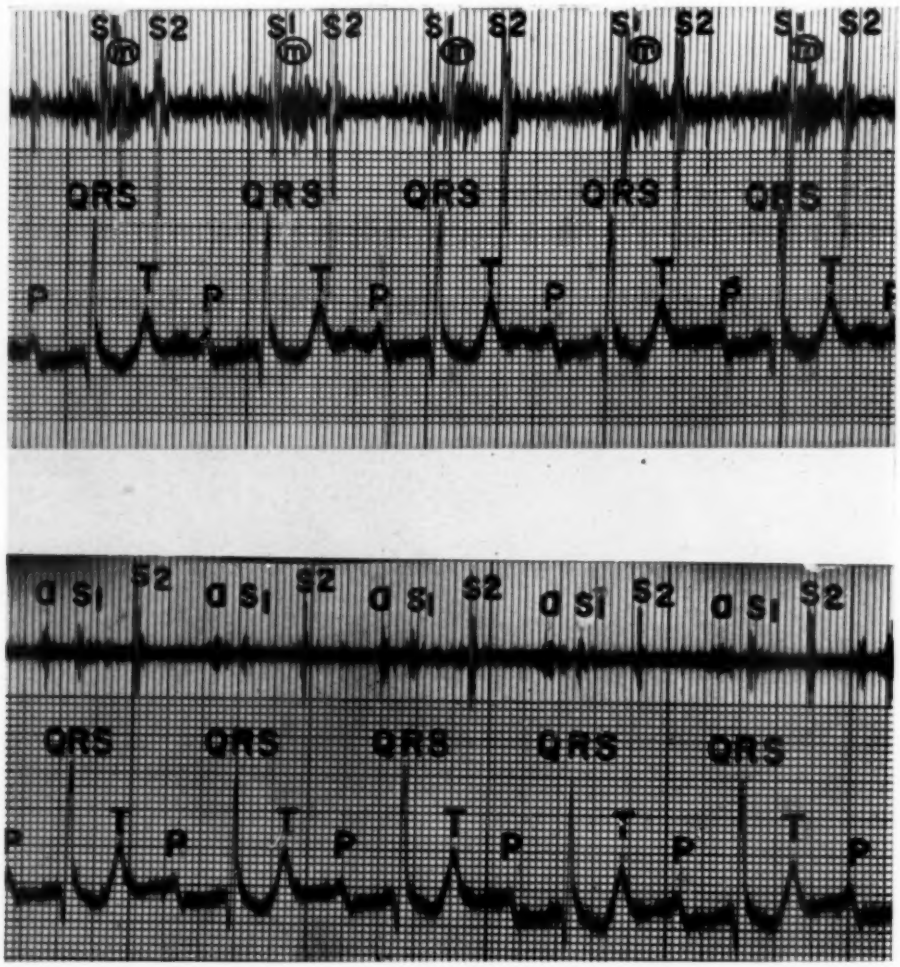

Fig. 2.—Phonocardiogram taken Aug. 10, 1953, at the time when the auricular sounds were audible. Upper tracing: Taken over the fourth anterior left intercostal space close to the sternum at maximum point of the systolic murmur (*M*). Lower tracing: Taken over the second left anterior intercostal space adjacent to the sternum where auricular sounds (*a*) were best heard.

Digitalis therapy was discontinued on August 11, 1953, and the first stage atrioventricular block perisisted. Gastriontestinal tract symptoms became a problem following prophylactic Aureomycin therapy for dental extractions, and a tracing on August 18, 1953, revealed auricular fibrillation with a poorly controlled ventricular rate. Digitalization was reinstituted at this

time. A 4:1 auricular flutter was noted on August 20, 1953 (Fig. 1, *G*), with return to the basic rhythm of auricular fibrillation on Sept. 2, 1953 (Fig. 2, *H*). There was no evidence of congestive failure at this time, and the nausea and diarrhea gradually subsided. On maintenance-digitalis therapy, the auricular fibrillation stabilized between 60 to 80 beats per minute. He remained completely asymptomatic and gradually became ambulatory over the succeeding four-week period. Well-controlled auricular fibrillation perisisted to date of hospital discharge in March, 1954.

DISCUSSION

It was thought that the cardiac abnormalities in this case were probably caused by arteriosclerosis and coronary artery disease; however, because of the sudden onset, a myocardial infarction could not be ruled out in spite of lack of definite evidence of this in serial electrocardiographic tracings. The possibility of a defect due to rupture of the septum following myocardial infarction was initially considered, but his excellent response to digitalization argued against a significant intracardiac shunt or mitral valve leaflet defect.[29]

A review of the seventy-one previously reported cases revealed an average age at time of onset of the complete block plus auricular flutter to be 60 years, with a range of 13 through 84 years. This occurred in fifty-seven males and fifteen females. The commonly suspected cause was arteriosclerotic heart disease in forty-two of the cases, and in twenty-five there was associated, pre-existing hypertension. Coronary insufficiency, myocardial infarction, rheumatic, syphilitic and congenital heart disease were etiologic factors in nine, five, five, six and three cases, respectively. Single cases were thought to be caused by thyrotoxicosis, coarctation of the aorta, and adhesive pericarditis. Those instances of block plus flutter occurring in people under 55 years of age were due to rheumatic, congenital, and syphilitic heart disease in all but four instances. Stokes-Adams episodes were observed in twenty-eight instances of the seventy-one cases, and evidence of congestive failure was found in thirty-one of the cases.

Auricular heart sounds were documented in five cases.[25,26] These were heard as rapid clicking, or tick-tack sounds over the base of the heart, usually in the right and left second intercostal spaces adjacent to the sternum. Complications of note were those of congestive failure in thirty-one of the cases, cerebral hemorrhage in three, and one case of a saddle embolus which was surgically removed.[24] Thirteen cases were followed for an average of three years after the original diagnosis was made, with one case living for eleven years.

Smith and Smith[21] believe that the prognosis of complete heart block plus flutter is probably the same as for uncomplicated complete block due to arteriosclerotic changes. In seven cases, autopsies revealed myocardial fibrosis involving the bundle of His.

A review of the electrocardiograms of the seventy-one cases of complete block plus flutter showed left bundle branch block associated in six and right bundle branch block present in four tracings. The QRS complexes were usually normal, although widening to 0.15 sec. was noted in ten of the cases.

The therapy most commonly employed was digitalis, with definite improvement in fifteen cases in whom congestive failure was present. It was without benefit in twelve cases. In our case, digitalis was of distinct benefit in the man-

agement of the congestive failure and may have altered the basic rhythm. Quinidine, when used, produced no improvement in ten cases and in the four instances of reported improvement, it restored sinus rhythm on three occasions with persistence of the complete block. Atropine, ephedrine, barium chloride, aminophylline, Paredrine, thyroxine, Adrenalin and pressure over the carotid sinus were all utilized without appreciable benefit.

Generally, it is thought that the association of complete heart block plus auricular flutter occurs mainly as a result of arteriosclerotic heart disease with rheumatic, congenital, and syphilitic heart disease playing only a minor etiologic role. Most cases occur in the older age group, and as stated by Brandman and associates,[19] Thorborg,[10] and Hanssen,[17] this type of arrhythmia probably occurs more frequently than is indicated by the relatively few cases reported in the literature. There has been no mention in the literature[30] and no indication in the case reported here that digitalis, when used judiciously, had any harmful effect on the heart block.

SUMMARY

A review of the literature of seventy-one cases of auricular flutter associated with complete heart block is presented. The incidence, age, etiology, electrocardiographic study, prognosis, and treatment are discussed.

A single case is reported in which unusual transient changes in rhythm were observed in serial electrocardiograms. Auricular sounds were demonstrated phonocardiographically. The case presented here is of particular interest, for several possible etiologic factors existed. These consisted of severe, arteriosclerotic heart disease with probable focal septal-wall infarction, although no diagnostic ECG evidence of the latter was documented. Serial ECG changes revealed conversion of the complete heart block with auricular flutter to first stage atrioventricular block, with the ultimate pattern of a well-controlled auricular fibrillation.

It is concluded that the association of complete heart block plus auricular flutter may be more common than realized, particularly in elderly patients with arteriosclerotic and coronary heart disease.

Digitalis therapy is of benefit in the majority of cases, since they are frequently complicated by congestive failure.

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TRANSIENT VENTRICULAR FIBRILLATION

VI. Observations on the Peripheral Arterial Pulse Pressures in the Course of Transient Ventricular Fibrillation During Established Auriculoventricular Dissociation

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THE existence of a transient form of ventricular fibrillation in man has been questioned by physiologists ever since fibrillar contractions of the heart were suspected to exist clinically.[1] Indeed so little is known about the intimate mechanism associated with ventricular arrhythmias and so dissimilar at times are the electrocardiograms interpreted as transient ventricular tachycardia, flutter, or fibrillation, that a classification similar to that of auricular arrhythmias is still wanting.

Sir Thomas Lewis has aptly remarked that ". . . to sum up the evidence and write down briefly the nature of these disturbances now included in the term ventricular fibrillation is difficult because the condition remains undefined."[2] Nevertheless, such irregularities of the ventricles especially when present during established auriculoventricular dissociation are of extreme clinical importance because they may occur in man in a recurrent and transient form in association with ineffective ventricular contractions, the so-called Stokes-Adams seizures.[3]

Since in animals the intraventricular and aortic pressure drops to zero when ventricular fibrillation sets in[4] it was thought worth while to try and correlate the electrocardiograms of the ventricular arrhythmias present during such seizures with peripheral arterial pressure changes in the hope that further enlightenment could be shed on these abnormal events.

REVIEW OF LITERATURE

Experimental Observations.—In questioning the presence of transient ventricular fibrillation, McWilliams[5] felt that some instances of assumed spontaneous recovery in the higher mammals and in man were probably not cases where true fibrillation had been fully established but a related though essentially a different condition which may be easily mistaken for ventricular fibrillation. These temporary conditions in the ventricles presenting many points of resemblance to true fibrillation consisted of a degree of incoordination of the ventricular musculature attended by a great reduction in the range of contraction movements and very little expulsion at each beat,

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a great fall of arterial pressure and a failure to recognize pulsations of the peripheral arteries. He applied the term "pseudofibrillation" to this condition and felt that it was impossible to distinguish it from true fibrillation by an examination of the arterial pulse.

With the advent of the electrocardiograph, records became available of ventricular fibrillation in the dog.[6] Levy and Lewis[7] described the successive changes in the heart's rhythm leading to ventricular fibrillation when they studied the combined effects of chloroform inhalations followed by intravenous injections of small doses of Adrenalin chloride in cats. They observed, at first, multiple premature beats of a particular form which increased in number and then formed groups. These presented at times a unidirectional, bidirectional, or polytopic type of ventricular tachycardia that suddenly changed to ventricular fibrillation with a rate of 400 to 800 oscillations of the galvanometer string per minute. The electrocardiograms were almost but not quite regular in incidence. With slower frequencies the individual undulations were irregular. They also noted a degree of waxing and waning in the excursions of the oscillations, a variability in their frequencies and occasional weak string movements as a result of "tone" changes in the heart muscle. Similar appearances were seen after experimental obstruction of the coronary arteries[8] and also when fibrillation was induced by faradic stimulation or by poisoning with digitalis. By whichever means fibrillation was induced, it was preceded by variable tachycardias of ventricular origin.

Later, Rothberger and Winterberg[9] registered electrical variations from points on the fibrillating ventricles of cats and dogs, comparing these complexes in the electrocardiograms obtained simultaneously, and found these to be occasionally regular and synchronous.

On the other hand, Kisch[10] in similar experiments noted a marked asynchronism between the frequency of the oscillations in the electrocardiogram as compared with the partial electrogram. However, the irregular individual oscillations were the most common finding; the regular, the rarest.

Recently, Wiggers[11] registered in dogs similar punctate unipolar leads simultaneously from three or four regions of the ventricles together with standard electrocardiograms. Analysis of his records revealed a lack of incidence in the direction, form, and amplitude of most corresponding waves. The tempo and regularity of the major deflections were also variable.

Wiggers also compared the intraventricular pressure curves and electrocardiograms of the natural fibrillary process of the ventricles in the exposed dog's heart following electrical shock with the actual movements of the ventricles shown in cinematographic records. For descriptive purposes he divided the course of this type of ventricular fibrillation into four stages.

(A) An *undulatory* stage lasting one or two seconds which consists of deflections in the electrocardiogram occupying an interval of 0.08 sec. or more. At such time, the ventricles undergo three to six undulatory contractions which may have the earmarks of premature systoles. He felt that only the first of these initial beats represented a true premature contraction. The remainder were caused by re-entrant beats. The intraventricular pressure curve associated with this initial premature beat was barely recognizable. The successive electrocardiographic complexes following this premature beat were of diminished periods and different configurations and associated with various types of intraventricular pressure changes. He thought that such pressure changes were most likely due to "atrial contractions." (B) A second, *convulsive* stage of incoordination followed, lasted from 15 to 40 sec., and averaged 600-750 oscillations per minute. It was characterized by more frequent waves of contractions which sweep over smaller sections of the ventricles. These still were powerful contractions but since all masses do not contract in phase, the intraventricular pressure curves are small, ill-defined, and resemble those attributed by him in the undulatory stage to atrial contractions. (For comparisons see his Figs. 1, *A* and *C*). Occasionally the electrocardiographic deflections of this stage became even more rapid, attaining a frequency of 1,560 per minute when they passed to a (C) stage, of *tremulous incoordination*, lasting 2 to 3 minutes. The electrocardiographic deflections increase frequently to a rate varying between 600 to 1,800 per minute and diminish in amplitude. These innumerable groups of contracting fibers finally fail in their contractility as a result of increasing anoxia, and a final stage of (D) *atonic fibrillation* sets in, characterized by the slow passage of feeble contractions. The amplitude of the electrocardiographic deflections diminishes continually until only a small oscillation remains visible, before there is a total cessation of ventricular activity.

Clinical Observations.—The first example of cardiac recovery from ventricular fibrillation in man was recorded by Robinson and Bredeck[12] although in 1915 Hoffman[13] had obtained a record in which a fibrillary period was in evidence but too short in duration to give significant clinical manifestations. Since then (up to January, 1952) there have been collected in the literature fifty-two patients with transient ventricular fibrillation.[14]

In reporting a patient whose ventricular fibrillation reverted to normal sinus rhythm, Dock[15] noted that the diagnosis of ventricular fibrillation could not be proposed with the assurance usual in classifying records of auricular arrhythmias. The literature reveals that certain deflections were designated as "ventricular flutter"[16,17] when the oscillations in the electrocardiograms were dentate and continuous and fairly regular in form, and as fibrillation they were rounded and irregular. He felt certain that we would have to content ourselves with the diagnosis of tachycardia for those cases where persistent heart sounds and other pulsatile activity of the ventricles are present, and fibrillation for those where gross mechanical arrest is associated with persistent oscillations. The more irregular and rapid these oscillations, the more certain it is that they are advanced disturbances in ventricular rhythm.

Again, Parkinson and his associates[18] divided patients with Stokes-Adams seizures due to ventricular arrhythmias into those with a high ventricular tachycardia (rate 200-500) usually with ventricular fibrillation followed by standstill, and at times without standstill, and those with low ventricular tachycardia alternating with standstill. He described the deflections of the high ventricular tachycardias as practically regular and at times with phasic variations. At high rates these merge into simple undulations. He felt that the term "ventricular flutter" need not be used, for the resemblance to flutter is superficial.

METHOD OF STUDY

The natural course of transient ventricular fibrillation during established auriculoventricular dissociation was studied clinically and with electrocardiograms in a male patient, aged 56 years, who was subject to recurrent attacks of syncope for over ten years. In determining the effects of procaine amide[19] on his cardiac mechanism it was deemed advisable to study also the influence of this drug on his blood pressure. For this reason, under local anesthesia and with aseptic precautions, a No. 22-gauge needle was inserted in his right femoral artery. This was attached to a Sanborn electromanometer, and pulse pressure tracings were obtained at the same time that continuous electrocardiograms were taken with standard Lead II. An attempt was made to synchronize the instruments, but there was a slight lag in the electrocardiograms as compared with the arterial pulse tracings. However, the information obtained was considered of sufficient accuracy for the events studied. Correlations were made during, prior, and subsequent to several syncopal seizures before, as well as after, the use of the drug which was responsible for the development of some of the arrhythmias studied.

THE PREFIBRILLARY PERIOD

Variations in the Idioventricular Mechanisms.—The preliminary disturbances that lead to transient ventricular fibrillation during established auriculoventricular dissociation consist at first of variations in the idioventricular rate and rhythm. The idioventricular pacemaker of the heart may be relatively "fixed" when the heart rate does not vary more than an average of five beats at the most[20,21] or it may be very "labile" as a result of the influences of the extrinsic nerves.[22] Its lability is characterized by either an acceleration of the basic ventricular rate consisting of a variety of mechanisms that have already been

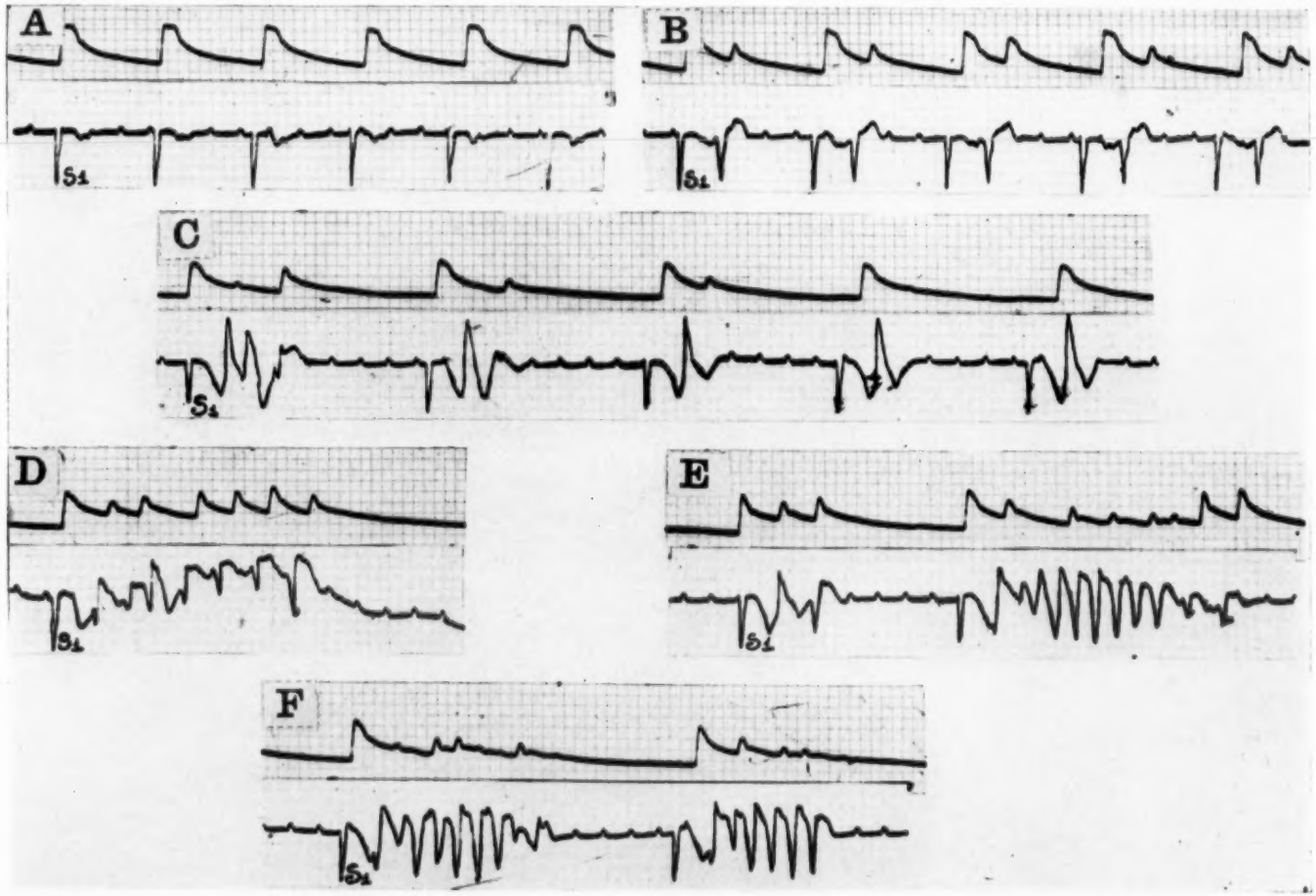

Fig. 1.—Upper curves are intraarterial pressures; the lower records represent Lead II of the electrocardiograms. *A*, The basic ventricular rhythm. *B*, The "initial" alternate premature beats of the ventricles. Note that the returning cycle after the premature beat is equal to the initial cycle. *C*, The alternate premature beats become frustrate and the peripheral pressures associated with them are low or absent. *D*, *E*, *F*, "Initial fibrillary periods" are associated at times with effective, low or diminishing and absent pulsations.

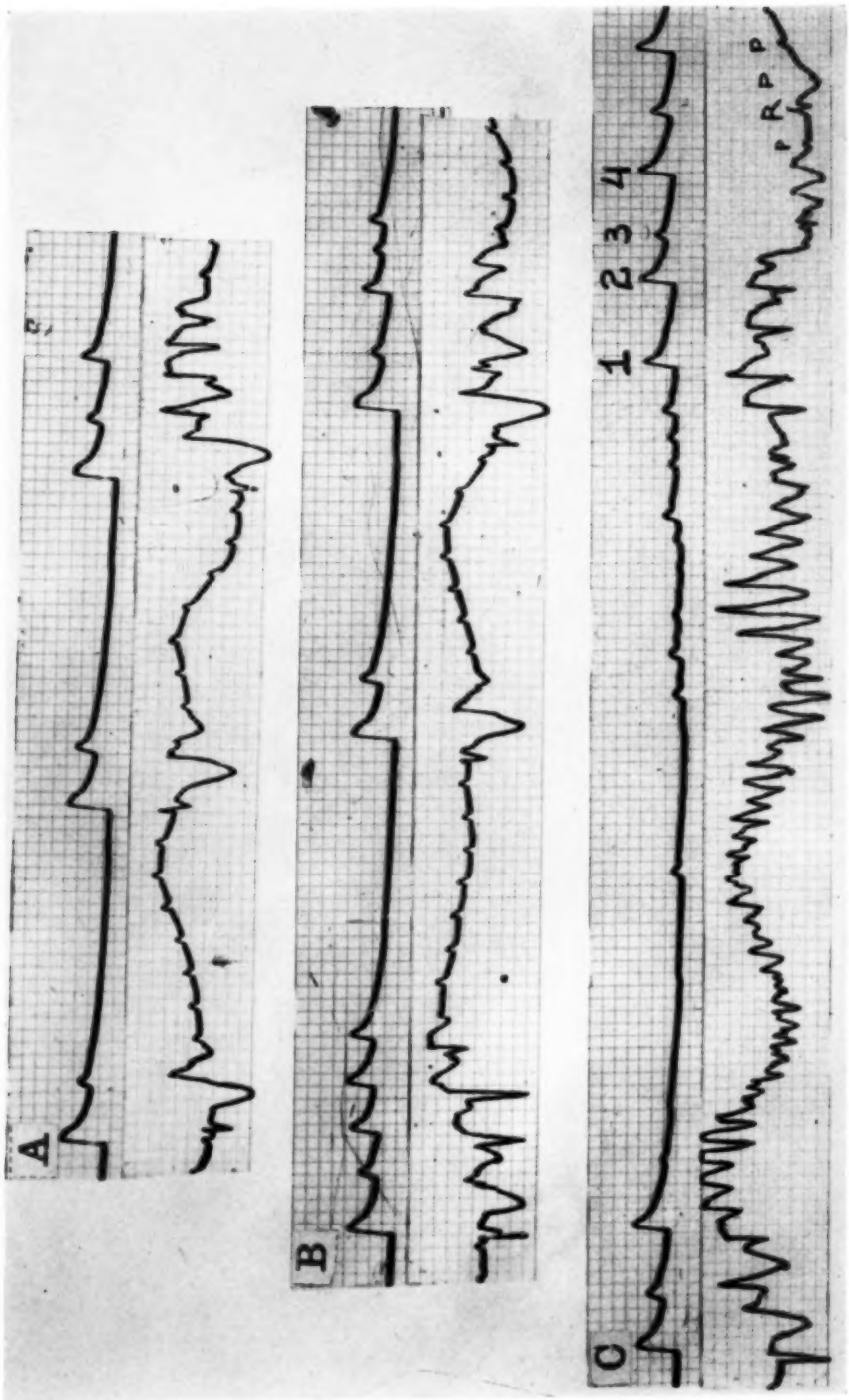

Fig. 2.—*A*, Deformed ventricular complexes may be associated with effective arterial pressure changes. Note increase in the duration of returning cycle following the premature beats of the ventricles. *B*, *C*. The "initial fibrillary periods" may be associated with a few effective beats and may be ended by effective beats. *1*, *2*, *3*, *4*. In between these the arterial pressure falls markedly.

described[23] or an alternate acceleration and retardation of the heart when ventricular rates as high as 34 beats per minute may drop abruptly to 16 beats and fluctuate from moment to moment for long periods at a time. In some instances the patients are conscious of these changes and complain of uneasiness in the chest, lightheadedness, a sensation of pounding in the head, and frequent nausea.

In the electrocardiograms obtained during this interval, the RS-T segments reveal unusual prolongations indicating a marked conduction disturbance within the ventricles. (In Fig. 1, compare the RS-T segments of S_1 in *A*, *B*, *C*, and *D*.) However, no variations were obtained in the peripheral arterial pulse pressures which were uniform from beat to beat (Fig. 1, *A*).

Initial Premature Beats of the Ventricles.—These preliminary disturbances in the rate and rhythm of the idioventricular pacemaker of the heart which may last from a few minutes to several days at a time facilitate the onset of transient ventricular fibrillation. This is invariably initiated by the appearance of premature beats of the ventricles. The intimate physico-chemical factors responsible for the appearance of such premature beats are still unknown.

In the early phases of the development of these arrhythmias, the electrocardiograms of the initial premature beats of the ventricles resemble most often the basic ventricular complexes (Fig. 1, *B*), and they are at a relatively fixed distance from moment to moment. The pause which follows these premature beats is usually shorter or equal to the interval between two basic beats. Undue prolongation of this interval occurs after the use of drugs that may affect the refractory period of the ventricles.[24] The arterial pressure curves associated with these initial premature beats are likewise equidistant from the pressure curves of the basic ventricular beats, but they are not of equal amplitude or duration from beat to beat. (Compare the pulse tracings of the first four premature beats in the Fig. 1, *B*.)

Deformed Ventricular Complexes in the Electrocardiograms of the Initial Premature Beats.—Of particular interest in this phase is the development in the electrocardiograms of deformed ventricular deflections with T waves, which increase markedly in size and exhibit on their ascending limbs only portions of the electrocardiograms of the initial premature beats (Fig. 2, *A*). Such graphic manifestations have never been observed with any other clinical conditions and have been found to herald a transient seizure of ventricular fibrillation. The arterial pressure curves associated with the initial premature beats of the ventricles of these deformed ventricular complexes are at first equidistant from those of the basic ventricular complexes (Fig. 2, *A*). They vary slightly in amplitude and duration. As this mechanism continues, however, many of these initial premature beats become frustrate, and no arterial pressures are registered in their presence (Fig. 1 C_1). It is difficult to know whether the changes in shape or direction of the initial premature beat of the ventricles which occur from time to time are an index of a change in the site of the origin of the ectopic focus.

Initial Fibrillary Periods of the Ventricles.—The perpetuation of the fibrillary process in man seems to be conditioned by the recurrent development of short

periods of fibrillation that may progressively increase in duration. Such a mechanism is unique for the human heart and has not been observed in the experimental animal.

At times there is added to these "initial" premature beats single widely aberrant ventricular complexes some higher and some lower in amplitude that resemble extrasystoles each separate and distinct from the other (Fig. 1, *D* and Fig. 2, *B*). These may be clearly heart at the apical region of the heart and felt at the pulse. They produce heart sounds that may be registered[25] and the arterial pressures may be often equal in amplitude though of shorter duration than those associated with the basic complexes. It is such groups of oscillations that because of their audibility and pulsatile phenomenon have been variously called "pre-fibrillary tachycardias."[26]

Frequently noted among these toward the end of the group are one or two ventricular deflections that resemble those of the basic ventricular complexes. Associated with these may be an arterial pressure curve that is larger in amplitude, though not in duration, than that of the basic ventricular complexes (Fig. 1, *E* and Fig. 2, *C*).

A second mechanism consists of widely aberrant oscillations without any distinct base line, at times diminishing in size from beat to beat (Fig. 1, *F*), at other times remaining the same size and often with deflections different from the others.

These periods vary in duration from two to twenty oscillations and as they increase progressively in number and recurrences, they herald a major seizure of ventricular fibrillation.

Only the first few of these beats may be audible at the apical region of the heart or palpable at the pulse. If such oscillations last for 6 sec. the patients merely shut their eyes. If they last 20 to 40 sec. momentary consciousness is lost and there is interruption of the trend of thought. Pallor sets in, and frequently there is sweating with an awareness of pains in the chest when the mechanism is restored to normal.

The arterial pressure curves registered at such times diminish progressively in amplitude and duration, but there is always some evidence of circulation present. (Fig. 2 *C*) Finally, each of these short periods may be terminated by one or two isolated deflections in the electrocardiograms different in shape and size from the other oscillations and associated with an arterial pressure curve that is equal in size and approaches in amplitude the basic ventricular curves (Fig. 2, $C^{1,2}$).

These initial fibrillary periods pose certain problems. The question arises whether they are the result of multiple extrasystoles from the same focus but registered in the electrocardiograms differently because of their different passage through the ventricles, or whether they are true fibrillary waves resulting in ventricular deflections that resemble premature beats of the ventricles. In the experimental animal, Wiggers felt that only the first of these oscillations is a premature beat, and the rest have a family resemblance to them but are in reality fibrillary waves forming the first undulatory stage.

FIBRILLARY PROCESS IN MAN

A review of several hundred examples of complete seizures of transient ventricular fibrillation, lasting from 40 sec. to 3 min. at a time, lends convincing evidence that true ectopic ventricular tachycardias or so-called ventricular tachysystoles never precede a period of transient ventricular fibrillation. The exceptions noted are in those instances where recurrent attacks of long duration may follow each other in rapid succession. At such times, the postfibrillary periods of asystole[27] may be succeeded by ventricular arrhythmias with rates as high as 160 beats per minute and regular in rhythm. These may be followed in turn after a few beats of the basic complexes by another seizure of transient ventricular fibrillation.

These facts are important to bear in mind, because in the experimental animal it is common to have a ventricular tachycardia terminate abruptly and be followed by ventricular fibrillation. On the other hand, it is not rare to note the presence of a transient seizure of ventricular fibrillation in man terminate abruptly and be followed by a true ectopic ventricular tachycardia (Fig. 5, *C*). These tachycardias are associated with good heart sounds and with beats that come through at the pulse regularly, even though the patient may remain in stupor or coma as a result of the previous seizure of ventricular fibrillation. Such changes are rather common in the course of these arrhythmias.

It is the presence of such tachycardias with audible pulsatile activity, which follow transient ventricular fibrillation associated with syncope, that have caused confusion in the recognition of the underlying cardiac mechanism responsible for syncopal attacks.

The size and form, the frequency, duration, and amplitude of the transient fibrillary process in man are unpredictable from moment to moment. In the same individual, the electrocardiographic deflections may differ from record to record and from day to day if the records are obtained with the same electrocardiographic leads (compare *A* and *B* in Fig. 5). The possibility suggests itself that if simultaneous leads were to be obtained during the fibrillary period in man, they would probably register different forms of oscillations in the respective leads, somewhat similar to the electrocardiograms obtained by Wiggers with unipolar leads.

What is pertinent, however, is that no matter what the form of the oscillations may be in the presence of these ventricular arrhythmias, with or without phasic variations, with deflections of high or low amplitude, with regular or irregular rhythms, and with variable rates from 80 to 460 beats per minute, the peripheral arterial pressure curves registered in their presence are of identical nature. The blood pressure falls below normal levels because of the diminished ventricular output, but there is always some form of pulsatile activity (Fig. 3, *A* and Fig. 4, *A* and *B*), unlike the experimental animal where the pressure falls to zero promptly upon the development of ventricular fibrillation. The arterial pressure curves bear no relationship to the rate of the electrocardiographic oscillations. They are irregular in rhythm from moment to moment and alternate in amplitude and duration between smaller and larger ones without any periodicity.

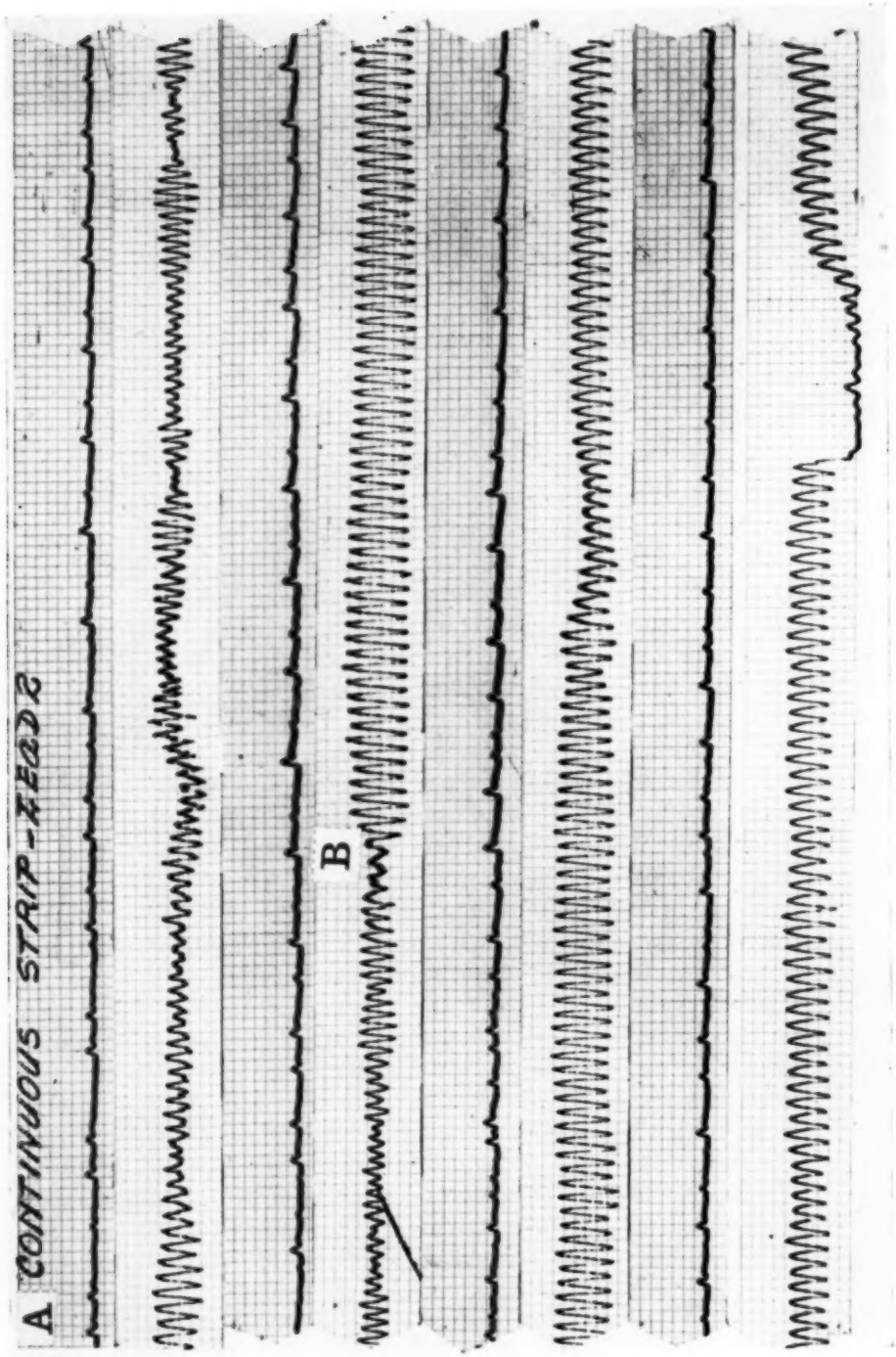

Fig. 3.—The arterial pressure falls but there is always some circulation during the presence of transient ventricular fibrillation, no matter what the rate, shape, or size of electrocardiographic deflections may reveal.

The smaller pulsations cannot be associated with atrial activity, since in the presence of P waves, cessation of ventricular action is associated with zero pressure. This may be best seen with complete asystole of the ventricles after the termination of a long seizure of ventricular fibrillation (Fig. 4, *B*).

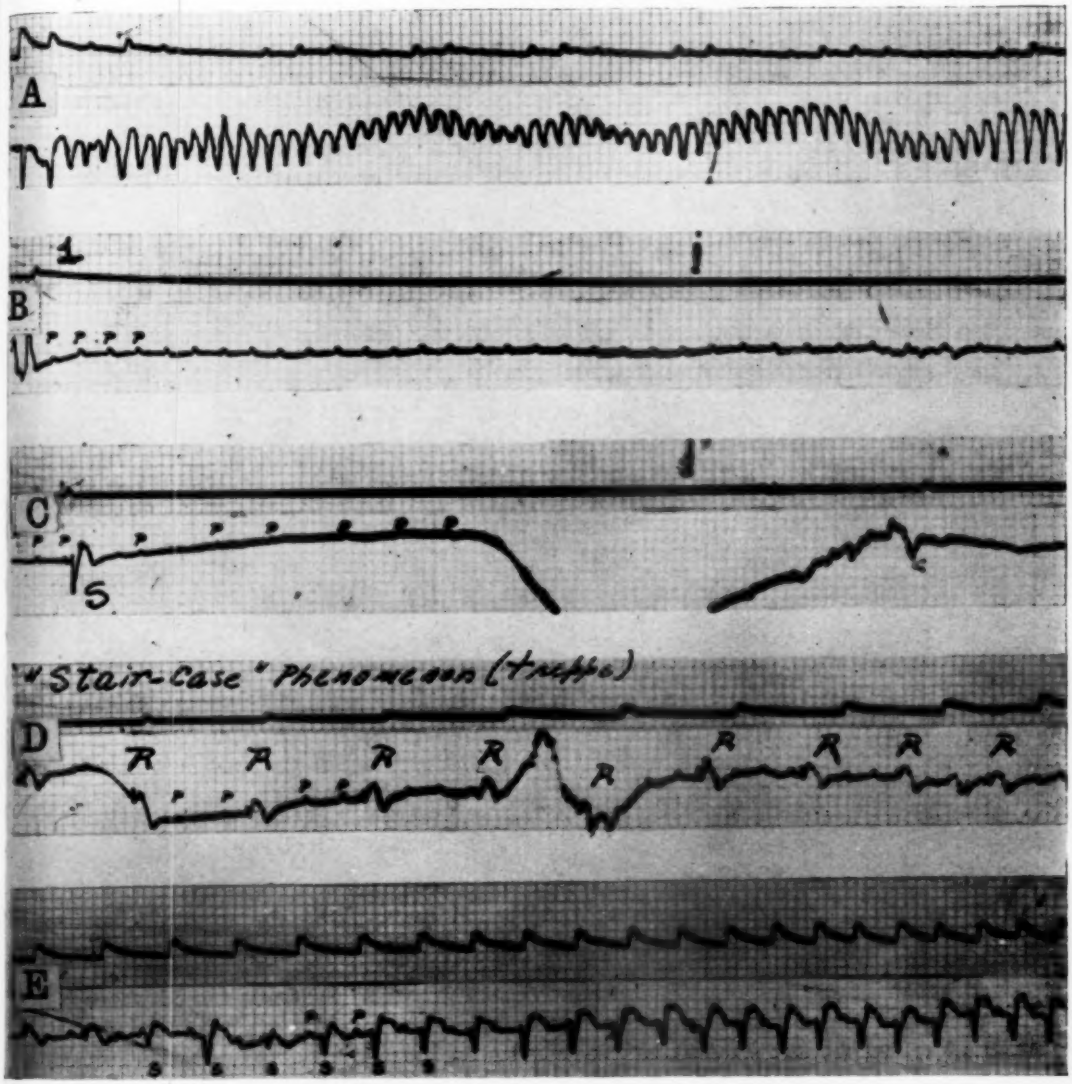

Fig. 4.—*A*, The femoral arterial pressure pulses fall to about one-half normal after repeated attacks. (Compare with Fig. 1, *A*.) *B*, The arterial pressures are zero during ventricular standstill even though the auricles are beating continuously. *C*, The auricles slow because of asphyxia. *D*, "Treppe" or "Staircase Phenomenon" associated with progressive increase in the arterial pressure curves as contractility is regained. *E*, The peripheral arterial pressures are normal during ventricular tachycardia.

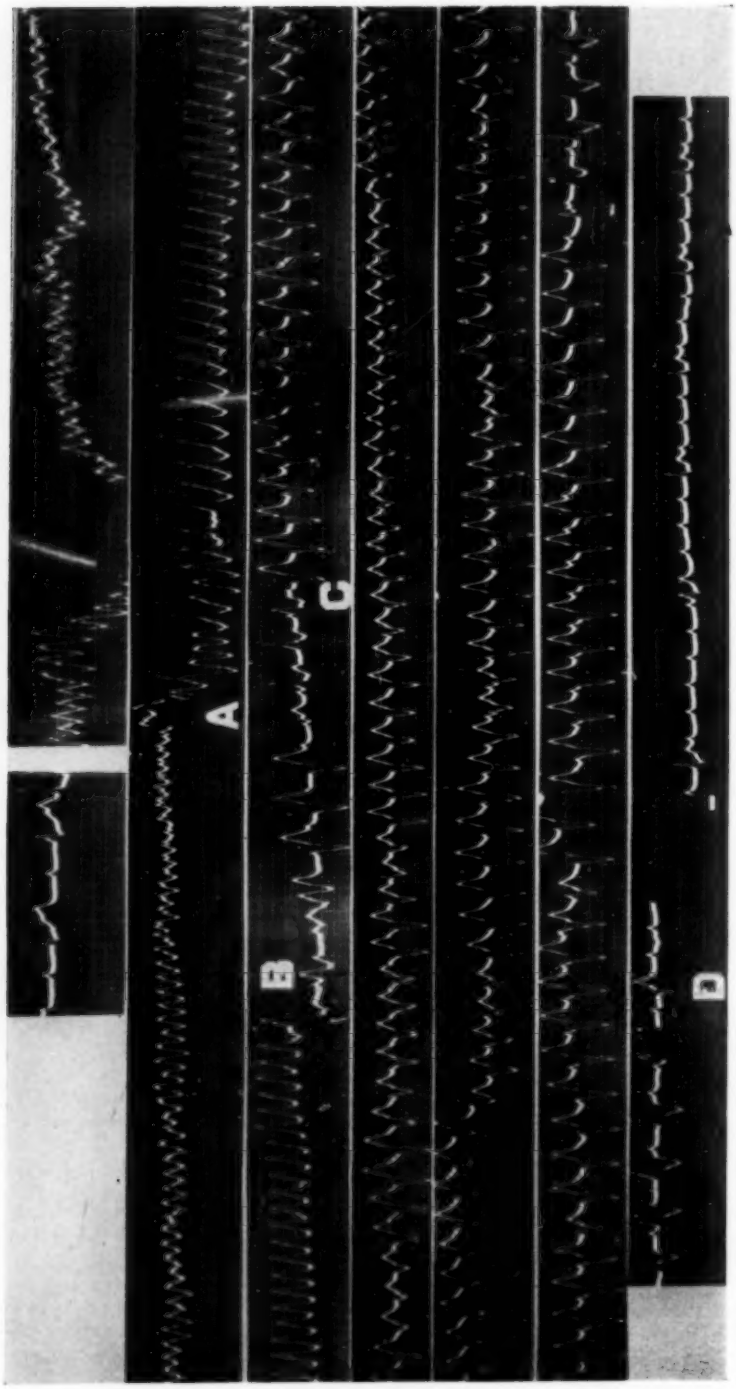

Fig. 5.—Transient ventricular fibrillation may be followed by a ventricular tachycardia before the return to the dominant rhythm present before the seizure.

That some form of pulsatile activity was present during fibrillary stages in man was suspected by Wenckebach and Winterberg.[28] Despite the absence of a clinical pulse and inaudibility of the heart sounds, they felt that the circulation was not entirely interrupted. Poor apical heart sounds cannot always be heard during convulsive seizures.

Termination of the Fibrillary Process in Man.—The manner in which transient ventricular fibrillation during established auriculoventricular dissociation is terminated and the basic rhythm resumed is dependent upon several factors. The number, nature, and duration of the perfibrillary periods must certainly play a part. If these short preliminary events are associated with ineffectual ventricular contractions, then asphyxial states resulting are likely to cause metabolic disturbances that influence all properties of the heart muscle, especially when a major seizure supervenes.

The usual and most common manner in which ventricular fibrillation may be terminated is by a short postundulatory pause with an immediate return of the basic and dominant rhythm. Prior to its termination at such times, the fibrillary process may be slow and exhibit wide electrocardiographic deflections, distinctly separated from each other and having a resemblance to the basic ventricular complexes. The arterial pressure curves increase progressively in size (Fig. 2, *C*-1, 2, 3) and reaching normal proportions, alternate in amplitude and duration for a few beats before they finally return to normal. It is likely that many of these terminal beats are premature beats of the ventricles, the last of which has a compensatory pause that forms part of the postundulatory period. The arterial pulse pressures associated with these are larger than those of the fibrillary groups, and there is the possibility that by flooding the coronary circulation they enable the heart to resume its own pacemaker during the short pause that follows. It is well known that a single premature beat of the ventricles may stop ventricular fibrillation.

Longer seizures or drugs have a profound effect on rhythmicity and contractility so that termination of the fibrillary period is associated with weak pulsatile activity in the arterial records, hardly greater in amplitude and duration than any of the larger pulsations present during fibrillation (Fig. 4, *B*-1).

POSTFIBRILLARY PERIOD

Long periods of ventricular fibrillation or recurrent attacks that may be followed by periods of ventricular tachycardia may be succeeded by a ventricular rate slower than the normal rhythm for some time after the attack. There may then ensue a gradual return of the idioventricular rate and rhythm that was present before the attack (Fig. 5, *D*). A fibrillary period may also end by complete cessation of ventricular activity or asystole of the whole heart lasting from 30 to 50 sec. and be followed for several minutes by progressively decreasing intervals of similar inactivity of the ventricles. Such periods during which the blood pressure falls to zero, and the circulation is at a standstill, judged by the total absence of pulsatile activity in the peripheral arterial curves, pose a far graver outlook than the fibrillary periods in themselves (Fig. 4, *B* and *C*).

Atrial activity may be present throughout these periods of asystole of the ventricles, at first, with a moderately rapid rate and then with a slower and irregular rhythm (Fig. 4, *C*) as the asphyxial state increases.

After an interval of such inactivity, the ventricles begin to beat again at first slowly and irregularly. In the electrocardiograms the idioventricular rhythm consists of aberrant ventricular complexes that vary from deflection to deflection but are associated in the arterial pulse tracings with steplike (treppe) progressions in the amplitude and duration of the respective beats (Fig. 4, *D*). It would appear that contractility of heart muscle is profoundly influenced by the asphyxial state so that revival of the heart and rhythmicity is retarted by the inability of the ventricles to contract normally.

These progressively increasing pulsatory changes finally return to a relatively normal level in the stage which follows standstill. This is characterized by an acceleration of the heart rate up to 160 beats per minute during the presence of auriculoventricular dissociation (Fig. 4, *E*). The contractions of the atria and their fortuitous presence before a ventricular complex in the electrocardiograms suggest at times the presence of a normal sinus rhythm as was shown by Cushny.[29]

SUMMARY AND CONCLUSIONS

1. Correlations were made between the clinical manifestations, electrocardiograms, and femoral arterial pressures of alterations in the rhythm of the heart prior, during, and subsequent to transient seizures of ventricular fibrillation with established auriculoventricular dissociation.

2. The alterations in the rhythm of the heart associated with such seizures may be divided into prefibrillary, fibrillary, and postfibrillary stages. The recording of any or all of these stages in any one patient should help in the recognition of the mechanism responsible for Stokes-Adams seizures associated with these abnormal rhythms.

3. The prefibrillary period may consist of (a) variations in the rate and rhythm of the idioventricular pacemaker of the heart; (b) the development of "initial" premature beats of the ventricles, at first appearing singly and then in groups; (c) the appearance of deformed ventricular complexes in the electrocardiograms with prolonged RS-T segments and progressively increasing T waves; and finally (d) the appearance of "initial" fibrillary periods that invariably follow the premature beats.

4. It was found that the femoral arterial pressure curves were normal during the presence of variations in the idioventricular pacemaker of the heart and in the early phases of the initial premature beats of the ventricles when they formed a bigeminal rhythm with the basic ventricular complexes. If the bigeminy persisted for any length of time, the arterial pressure curves associated with the initial premature beats became smaller and varied in amplitude and duration.

5. The femoral arterial pressure curves obtained during the presence of deformed ventricular complexes in the electrocardiogram revealed changes similar to those noted with any other initial premature beats indicating that they did not represent fractionated systoles but effective ventricular contractions.

6. The "initial" fibrillary periods revealed several types of mechanisms. (a) Groups of from two to six premature beats of the ventricles, distinctly separated from each other, were associated with effective femoral arterial pressure curves although these were slightly variable in amplitude and duration; (b) groups of widely aberrant oscillations with no distinct base line and following an effective premature beat revealed femoral arterial pressures that diminished progressively in amplitude and duration from beat to beat; and (c) groups of irregular ventricular oscillations each different from the other with at first diminishing pressure curves but terminating in effective ventricular contractions with pressure curves equal or greater than those of the basic ventricular beats.

7. The fibrillary process in man consists in the electrocardiograms of ventricular oscillations that are both regular and irregular in rhythm with rates varying from 160 to 460 beats per minute. None of these oscillations have a distinct base line, and they may be wide or narrow in duration, high or low in amplitude, regular or irregular in sequence, but they are always associated with a definite peripheral arterial pressure curve even though their beating may be inaudible and not palpable clinically. The arterial pressure curves are markedly diminished in height and duration from moment to moment as compared with the normal. The diminished ventricular output associated with these is responsible for the syncopal attacks.

8. Transient ventricular fibrillation may be ended by a postundulatory pause, by a ventricular tachycardia, or ventricular standstill before the basic rhythm is gradually resumed.

9. The atria maintain their regular rate and rhythm during such seizures except in the longer periods when they may be slowed to an irregular rhythm and at times to standstill.

10. The postfibrillary tachycardias are all associated with effective ventricular contractions as may be judged by their normal peripheral arterial pressures.

11. In the postfibrillary periods with asystole of the ventricles, the arterial curves are totally absent and the pressure falls to zero. The atrial contractions which persist do not play any part in the formation of the pressure curves.

12. Transient ventricular fibrillation in man is a definite entity associated with a markedly diminished ventricular output of blood. Complete cessation of the circulation is present only during the periods of ventricular asystole that may follow transient ventricular fibrillation or tachycardia.

13. The survival of patients with transient seizures of ventricular fibrillation during established auriculoventricular dissociation is due to the presence of some circulatory blood flow during the fibrillary stages as compared with total absence of circulation in course of standstill of the ventricles.

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TRICUSPID STENOSIS: CLINICAL AND PHYSIOLOGIC EVALUATION

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STENOSIS of the tricuspid valve represents a cardiovascular defect that is amenable to surgical correction by established operative techniques. There have been, however, only two reported instances of tricuspid commissurotomy.[1,2] The rarity of tricuspid valve surgery compared to mitral valve surgery is a result not only of the infrequent occurrence of significant tricuspid stenosis but, more important, a result of the invariable association of tricuspid stenosis with lesions of other valves. This multivalvular involvement often obscures the recognition of the tricuspid lesion.

Autopsy studies have demonstrated the presence of tricuspid stenosis in ten[3] to fifteen[4] per cent of patients with valvular rheumatic heart disease. Although it is probable that many of these instances of tricuspid stenosis described at autopsy were not of such severity as to warrant surgical intervention, nevertheless the impression remains that this valvular defect is not rare. These studies have also demonstrated that tricuspid stenosis was almost invariably accompanied by mitral valve lesions and frequently also by aortic valve involvement. The occurrence of rheumatic tricuspid stenosis as an isolated lesion,[5] as a lesion accompanied only with pulmonic valve lesions,[6] or resulting from etiologic factors other than rheumatic fever,[7,8] is of such rarity as to preclude consideration.

Tricuspid stenosis therefore constitutes only one element of a widespread rheumatic valvulitis. Patients with this lesion consequently usually present evidence of advanced cardiac disease and fall into a Class IV category. As such these patients represent poor candidates for surgical therapy. Moreover, the nature of the accompanying mitral and aortic valve defects frequently in themselves present contraindications to surgery.

Diagnostic difficulties are presented by such factors as the similarity in the quality and location of the auscultatory manifestations of lesions of the tricuspid and mitral valves, by the absence or lack of specificity of the peripheral manifestations of tricuspid stenosis, and by the paucity of hemodynamic studies of this lesion.

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This report consists of a presentation of the studies in three patients with varying degrees of tricuspid stenosis in whom surgical therapy was instituted. The stenosis of the tricuspid valve in two of these patients was of only moderate degree and was not amenable to correction by surgery. In the third patient, "tight" tricuspid stenosis was present and was partially corrected by finger fracture commissurotomy. The diagnostic studies are reviewed in an attempt to establish criteria for recognition of the occasional instance of surgical tricuspid stenosis.

CASE REPORTS

CASE 1.—R. W., a 24-year-old white man had polyarthritis at age six years and chorea following scarlet fever at age seven years. Valvular heart disease was detected at nine years of age. The patient led an active normal existence until age 18 years, at which time there was an onset of shortness of breath and palpitation on exertion. Episodes of massive pulmonary hemorrhage occurred at ages 19 and 21 years, necessitating hospitalization on each occasion. At age 21 the patient noted the onset of epigastric pain, pain in the back of the neck, and fullness and pulsations in the neck on exertion. Examination during hospitalization at age 21 revealed an enlarged heart, with auscultatory evidence of mitral stenosis, an enlarged liver, and an electrocardiogram demonstrating a right bundle branch block pattern. There was symptomatic improvement following digitalization and the patient was able to return to full-time work. A progressive decrease in exercise tolerance took place so that by the age of 24 years the patient could walk only two blocks without distress.

Physical examination revealed presystolic pulsations in the deep jugular neck veins with the patient in the erect position. Funduscopic examination showed engorgement and tortuosity of the retinal veins. The left border of cardiac dullness was at the left anterior axillary line. On auscultation a Grade 3, somewhat rough and blowing systolic murmur was audible along the lower left sternal border and to the apex. A medium-pitched, diastolic murmur of Grade 2 intensity was present at the apex and at the left sternal border in the fourth and fifth intercostal spaces. The lungs were clear to auscultation and percussion. The liver edge was palpable 5 cm. below the right costal margin and was moderately tender.

Fluoroscopic examination demonstrated enlargement of the left atrium and considerable enlargement of the right atrium and right ventricle. The electrocardiogram showed a pattern of a right bundle branch block with right ventricular hypertrophy. Broad P waves of increased amplitude in the right-sided chest leads suggested right atrial enlargement.

Venous cardiac catheterization was performed as described previously with pressures recorded by means of Statham strain gauges and a Hathaway recording apparatus.[11] The results of these catheterization studies are summarized in Table I. Elevated pulmonary arterial and pulmonary "capillary" pressures were present. The right atrial pressure at rest (Fig. 1,*A*) was considerably elevated with pressure peaks occurring during the period of ventricular systole and during right atrial systole. The enlarged *a* waves were the dominant waves of the resting right atrial pressure pattern. The pressure gradient between the right atrium and right ventricle during early ventricular diastole was quite small, being 2 mm. Hg. After exercise (Fig. 1,*B*) a complete change in the right atrial pressure pattern occurred with the dominant wave rising during ventricular systole thus representing tricuspid insufficiency. The *a* wave was relatively small, falling on the downstroke of this high insufficiency wave. The cardiac index was low at rest and rose only slightly on exercise. The arteriovenous oxygen difference was considerably increased at rest with a marked further increment on exercise.

Thoracotomy was performed using a transverse sternal splitting incision. A marked drop in blood pressure occurred while preparing the left atrial appendage for digital entry, and the operation was discontinued. Peripheral vascular collapse persisted, and the patient died 48 hours postoperatively. Post-mortem examination revealed a heart weighing 650 grams. The right atrium was considerably dilated and hypertrophied. The tricuspid valve leaflets were thickened, and the valve orifice narrowed, measuring only 7.5 cm. in circumference; however, the effect of the valve disease was such as to result in a predominant insufficiency. The right ventricle was

dilated, and the wall measured 6 mm. in thickness. The mitral valve was thickened, and the orifice narrowed to admit only the tip of the index finger. The aortic valve was thickened and opaque. Microscopic examination did not show evidence of active rheumatic carditis.

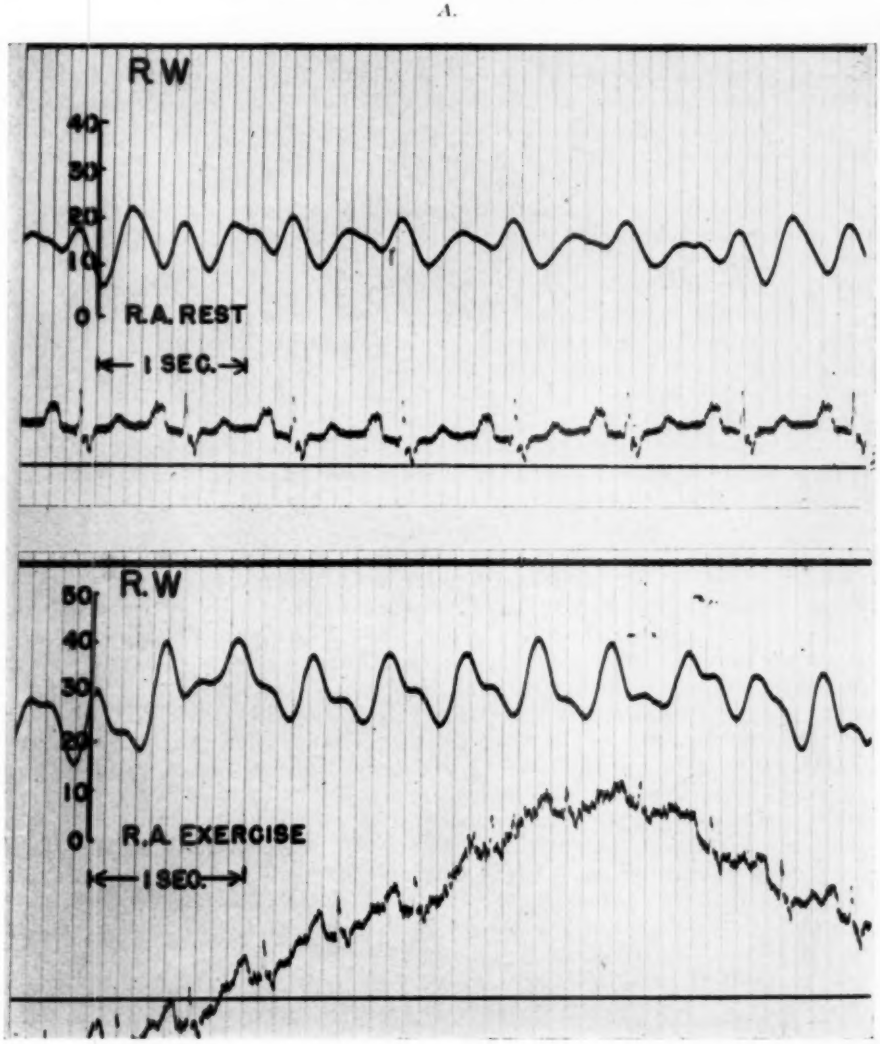


Fig. 1.—Case 1. *A*, Right atrial pressure at rest. *B*, Right atrial pressure following exercise. The electrocardiogram is standard Lead II.

CASE 2.—F. Z., a 38-year-old white woman had recurrent bouts of tonsillitis, ear infections, and spontaneous epistaxis during childhood. At 12 years of age there was an onset of ease of fatigue and exertional dyspnea. However, the patient was able to work, bear and raise three children, and do her housework until the age of 36 years. At that time there was an increase in the severity of the weakness and dyspnea. A diagnosis of valvular heart disease was first made at that time. At age 37 there was a further exacerbation of symptoms with episodes of paroxysmal nocturnal dyspnea and orthopnea, and the onset of swelling of the abdomen. There was moderate improvement following digitalization; however, two periods of hospitalization were required during the year. At the time of examination the patient's exercise tolerance was limited to one block at a very slow pace and to the performance of light household duties.

Physical examination revealed a thin, chronically ill woman with a violaceous hue over the malar eminences. A presystolic pulsation was noted in the deep cervical veins in the erect position. The heart was enlarged to percussion, both to the left and right. Auscultation revealed a high-pitched, blowing diastolic murmur along the left sternal border. A rough Grade 3, high-pitched, systolic murmur was present in the fourth and fifth left intercostal spaces at the sternal border and was also audible at the apex, although with decreased intensity. This murmur was followed by a medium-pitched murmur throughout diastole. At the apex the diastolic murmur was of decreased intensity and of lower pitch. The murmurs over the tricuspid area increased in intensity during inspiration. The inferior margin of the liver was palpable 6 cm. below the right costal margin, and there was pitting edema of the ankles.

The electrocardiogram revealed a sinus rhythm with a pattern of right ventricular and right atrial hypertrophy. Fluoroscopic examination showed considerable enlargement of the right atrium and moderate enlargement of the right ventricle and left atrium. The superior vena cava was dilated and pulsating.

Cardiac catheterization was performed on April 6, 1953 (Table I). Elevated pulmonary arterial and pulmonary "capillary" pressures were present. The resting right atrial pressure pattern was abnormal in amplitude and configuration; pressure waves occurred during ventricular systole and in late ventricular diastole at the time of right atrial systole (Fig. 2). There was only a small pressure gradient of 3 mm. Hg between the right atrium and right ventricle in early diastole. Following exercise, there was a further rise in the mean right atrial pressure with an accentuation of the pressure wave occurring during ventricular systole. The dominant pressure wave on exercise therefore was that of tricuspid insufficiency. The resting cardiac index was markedly reduced to 0.8 L./min./M.^{2}, and the arteriovenous oxygen difference was increased to 104.6 c.c./L.

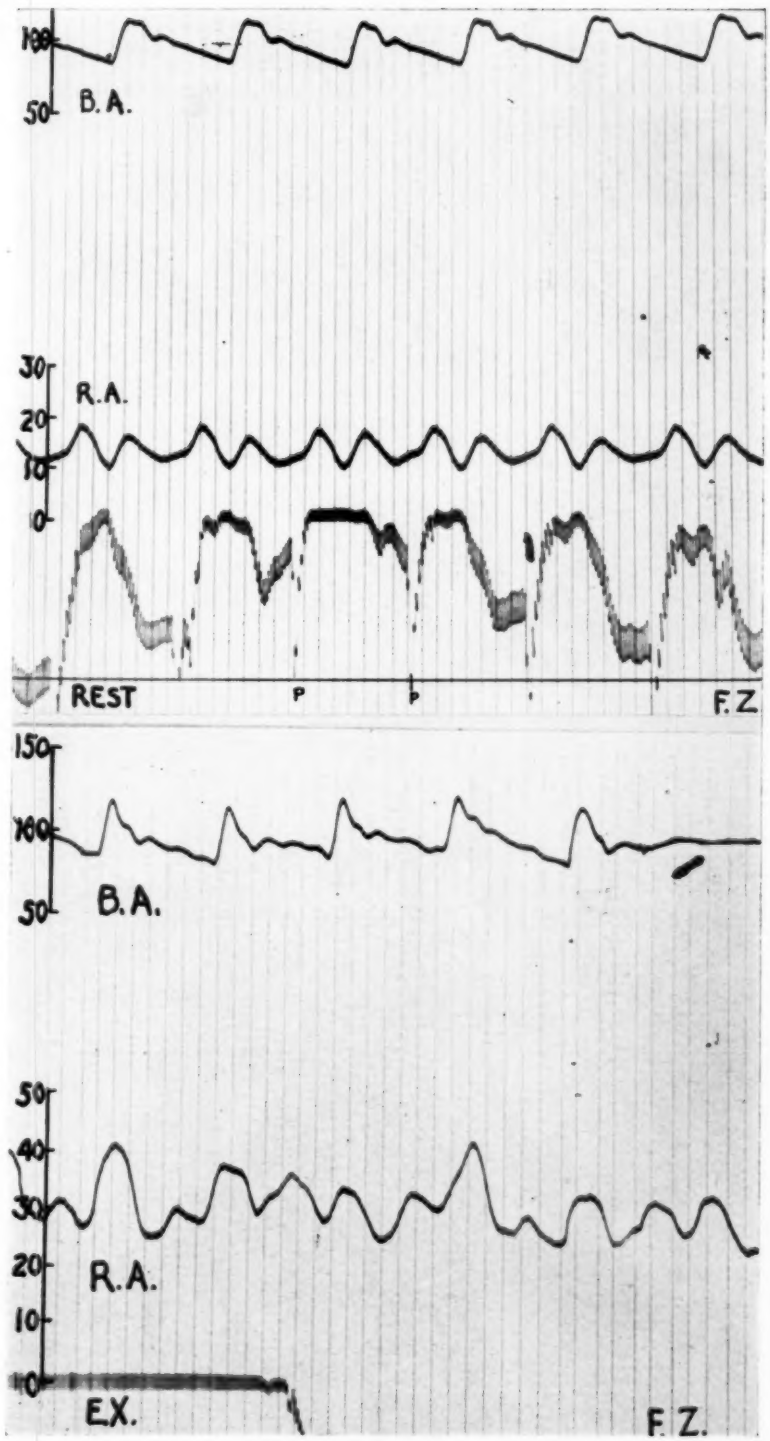
On May 19, 1953, a thoracotomy was performed using a transverse sternal splitting incision. The left atrium was moderately enlarged, the right ventricle considerably enlarged, and the right atrium greatly dilated. A tight mitral valve orifice was palpated, not admitting the tip of the index finger. This orifice was dilated to admit two fingers. The tricuspid valve was only moderately stenotic, admitting one and one-half fingers, and a forceful regurgitant jet was palpable. This orifice was widened slightly, and an unsuccessful attempt made to reduce the amount of regurgitation by an indirect plastic procedure. Microscopic examination of the tissue from the left and right auricles showed no evidence of active rheumatic carditis. Atrial fibrillation occurred postoperatively which slowed to atrial flutter and then reverted to a normal sinus rhythm. The postoperative course was also complicated by progression of the existing congestive failure.

Six months following the operation the patient was performing all household activities, and her exercise tolerance was increased markedly. Physical examination revealed a well-nourished woman with a normal complexion and no dependent edema. There was no distention or pulsation in the neck veins. On cardiac auscultation the high-pitched blowing diastolic murmur along the left sternal border had increased as compared to the preoperative intensity. A Grade 1 systolic murmur was heard in the left fourth intercostal space. A faint low-pitched murmur was audible over the tricuspid and mitral areas.

CASE 3.—M. C., a 43-year-old white woman experienced fever and severe migrating polyarthritis at age 14 years with the onset immediately following an attack of scarlet fever. A second severe episode of polyarthritis occurred at age 18. From age 20 to 32 years, the patient carried eight pregnancies to term and had two spontaneous abortions. During the last pregnancy at the age of 32 the patient noted the onset of ease of fatigue, exertional dyspnea, and episodes of paroxysmal nocturnal dyspnea. At the age of 33 years, there was a recurrence of fever and migrating polyarthritis which persisted for five months. Following this, the patient noted substernal and precordial pain on exertion and was aware of palpitation. There was an increase in the severity of these symptoms at age 40 with the onset of slight dependent edema and orthopnea. At the age of 42, there was a further exacerbation of symptoms with an onset of swelling of the abdomen, pain in the upper abdomen, and a sense of fullness in the neck. At the time of the preoperative studies, the patient's exercise tolerance was limited to one block.

Physical examination revealed a chronically ill woman lying flat in bed without discomfort. There was pitting edema of the ankles and a violaceous hue to the face. The retinal veins were dilated and tortuous. The deep cervical veins were distended, and a systolic pulse wave was

A.



B.

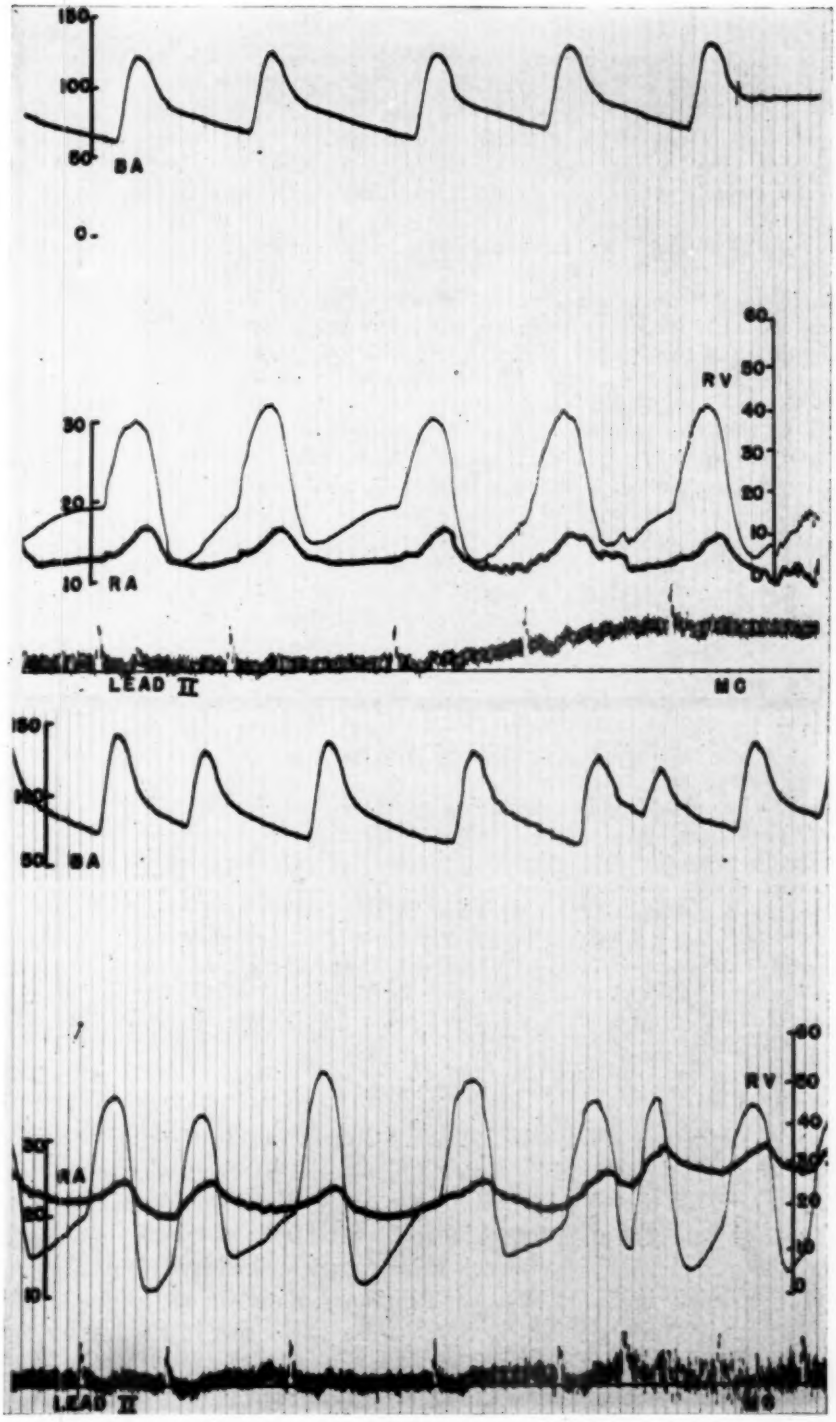
Fig. 2.—Case 2. *A*, Right atrial and brachial artery pressure at rest. *B*, Right atrial and brachial artery pressure after exercise. The electrocardiogram is from an intracavitary lead in the right atrium. The prominent downward deflections are P waves.

TABLE I

PATIENT AGE SEX	CONDITION OF STUDY	OXYGEN CONTENT C.C./L. OXYGEN SATURATION (%)		ARTERIO-VENOUS OXYGEN DIFFERENCE C.C./L.	CARDIAC OUTPUT C.C./MIN.	CARDIAC INDEX L./MIN./M.^{2}	PRESSURE MM. HG								
							RIGHT ATRIUM			RIGHT VENTRICLE			PULMONARY ARTERY	PULMONARY "CAPILLARY"	BRACHIAL ARTERY
		BRACHIAL ARTERY	PULMONARY ARTERY				SYSTOLE	EARLY DIASTOLE	LATE DIASTOLE	SYSTOLE	EARLY DIASTOLE	LATE DIASTOLE	SYST./DIAST. MEAN	MEAN	SYST./DIAST.
1. R.W., 24 yr., male	Rest	210.3 95.4%	124.3 56.3%	86.0	3620	1.9	20	12	20	69	10	—	73 51 — 40	20	120 — 90
	Exercise	*	47.8 21.7%	162.5	4140	2.2	38	24	22	—	—	—	86 65 — 55	25	—
2. F.Z., 38 yr., female	Rest	187.4 90.7%	82.8 40.1%	104.6	1320	0.8	17	12	19	78	9	12	77 44 — 43	20	124 — 84
	Exercise	—	—	—	—	—	29	21	26	—	—	—	—	—	—
3. M.C., 43 yr., female	Pre-op. Rest	197.1 93.8%	120.1 57.2%	77.0	4120	2.2	17	14	14	40	5	15	40 29 — 23	19	122 — 65
	Pre-op. Exercise	202.7 96.5%	97.6 46.5%	105.1	5120	2.7	25	20	21	53	3	20	50 35 — 27	24	130 — 72
	Post-op. Rest	164.0 91.4%	102.0 56.9%	62.0	4980	2.8	15	11	11	27	8	11	33 24 — 19	—	115 — 60

*Sample unsatisfactory. No significant change from resting value assumed.

A.



C.

Fig. 3.—Case 3. *A*, Right atrial, right ventricular, and brachial artery pressure at rest and *B*, following exercise. The scale on the lower left in each panel applies to the right atrial pressure.

present. The heart was enlarged to the left and to the right on percussion. On auscultation, a Grade 3, medium-pitched, somewhat rough, diastolic murmur was audible beneath the xiphoid process and at the left sternal border in the fourth and fifth intercostal spaces. A Grade 1 high-pitched, blowing systolic murmur was present in this same area. There was an increase in the intensity of these murmurs during inspiration. A diastolic murmur was audible at the apex with a lower pitch than the murmur present in the tricuspid area. A high-pitched, blowing, systolic murmur of Grade 1 intensity was also audible at the apex. The lungs were clear to auscultation and percussion. The liver was enlarged 8 cm. downward and was tender.

The electrocardiogram revealed atrial fibrillation and digitalis effect. There was no evidence of right ventricular hypertrophy. Fluoroscopic examination showed enlargement of the right and left atria, right ventricle, and the superior vena cava. The lung fields and costophrenic angles were clear.

The results of venous cardiac catheterization are summarized in Table I. Simultaneous right atrial and right ventricular pressures were determined using a double lumen catheter. An elevated right atrial pressure was present at rest with a single pulse wave noted at the time of ventricular systole (Fig. 3,*A*). The right ventricular pressure was moderately elevated during systole, fell to near normal levels in early diastole, and rose slowly to an elevated end diastolic level. There was accordingly a pressure gradient between the right atrium and right ventricle in early diastole of 9 mm. Hg. After exercise there was a further elevation and an increase in the atrio-ventricular pressure gradient in early diastole to 17 mm. Hg (Fig. 3,*B*). The arteriovenous oxygen difference was increased, and the cardiac index was low with little rise following exercise.

On Oct. 1, 1953, digital valvuloplasty of the mitral and tricuspid valves was accomplished through a transverse sternal splitting anterior thoracotomy. The mitral valve was stenotic, barely admitting the tip of the index finger. This orifice was dilated to admit one and one-half fingers. The right atrium was considerably enlarged, and the tricuspid valve orifice was also narrowed to admit only the tip of the index finger. The posterolateral commissure was fractured so that two fingers could be admitted through this valve orifice.

Histologic examination of the left atrial appendage revealed cellular aggregates resembling Aschoff bodies.

The postoperative course was complicated by chest pain, cough, and increasing fluid retention which persisted for three weeks.

Postoperative venous cardiac catheterization was performed on Nov. 9, 1953. A moderate decrease in pressure was present at all levels as compared to the preoperative values. The pressure gradient between the right atrium and right ventricle had decreased to 3 mm. Hg during early diastole.

Since operation there has been a gradual increase in the patient's activities so that two months following surgery she was able to perform most of her household tasks. Physical examination revealed a decrease in intensity of the systolic and diastolic murmurs in the left fourth and fifth intercostal spaces and an absence of the low-pitched apical diastolic murmur. The inferior margin of the liver was palpable 2 cm. below the right costal margin. The dependent edema had disappeared.

DISCUSSION

Clinical Aspects of Tricuspid Stenosis.—In contrast to the patients described by Ferrer and associates[9] and by Trace and associates,[2] the patients in this group presented many of the classical clinical features of tricuspid valve lesions. A history of right upper quadrant pain and ascites was obtained, and awareness of pulsations or distention in the neck veins was described by two of the patients. These findings early in the course of the disease before the occurrence of obvious signs of congestive failure are considered to be distinctive in suggesting primary tricuspid involvement.

The typical stasis cyanosis of the facies was present in two patients, although the arterial oxygen saturation was normal. Murmurs were present over the

tricuspid area in all patients and tended to increase in intensity during inspiration as described by Carvallo.[10] The diastolic murmur of triscuspid stenosis was higher in pitch and more rough in quality than the apical diastolic murmur of mitral stenosis. The systolic murmur of tricuspid insufficiency was similar in quality to that of mitral insufficiency with the possible exception of giving an auditory sensation of being closer to the ear. However, the location of the murmur of tricuspid insufficiency along the lower left sternal border was usually of sufficient valve to permit differentiation from the murmur of mitral insufficency. A precise differentiation of the murmur of tricuspid insufficiency from the murmur of mitral insufficiency is essential in determining operability. The presence of significant mitral insufficiency eliminates the possibility of beneficial surgical therapy, whereas tricuspid insufficiency does not necessarily contraindicate correction of a "tight" mitral stenosis. This fact is well demonstrated in Case 2.

The deep cervical veins were distended and pulsating in all three patients. The presence of a presystolic venous pulse wave in the two patients with sinus rhythm proved to be an unreliable sign of surgical tricuspid stenosis. Dominant tricuspid insufficiency was demonstrated in both patients at surgery or at autopsy. Considerable hepatic enlargement was present in all patients but no definite intrinsic hepatic pulsations were detectable.

Fluoroscopy revealed evidence of prominence of the superior vena cava and enlargement of the right atrium. These findings were suggestive of tricuspid involvement.

Thus, in this group of patients the usual clinical studies permitted the diagnosis of tricuspid valve disease, but were not sufficiently precise to permit the diagnosis of "tight" tricuspid stenosis.

Physiologic Aspects of Tricuspid Stenosis.—The level of the pulmonary artery pressure and the pulmonary "capillary" pressure were of value mainly in evaluating the degree of mitral valve involvement. However, it is of interest to note that in Case 3 with the significant tricuspid stenosis, the pulmonary artery pressure was only slightly elevated.

An analysis of the characteristics of the resting right atrial pressure pattern was found to be inadequate in determining the presence of dominant tricuspid stenosis. Atrial fibrillation was present in Case 3 so that the atrial pressure pattern consisted only of a high mean pressure with a single systolic wave. In Cases 1 and 2 with a sinus rhythm, the dominant wave at rest was an *a* wave. This finding has been considered to be a diagnostic feature of tricuspid stenosis. The subsequent course demonstrated that the stenosis in these patients was relatively mild and that insufficiency was the major defect. The occurrence of prominent *a* waves in situations other than tricuspid stenosis has been discussed in a previous study and is again demonstrated to be nonspecific in the diagnosis of tricuspid stenosis.[12] After exercise in Cases 1 and 2 the presence of a high regurgitation wave is shown with an approach to a "ventricularization" pattern. Thus the effect of exercise on the right atrial pressure wave is important in determining the significance of the tricuspid insufficiency.

Specific diagnostic valve was derived from the analysis of the pressure gradient between the right ventricle and the right atrium. This evaluation was more satisfactorily accomplished with the use of a double lumen catheter than by the drawback from right ventricle to right atrium with a single lumen catheter. In Case 3 a high pressure gradient between the right atrium and right ventricle was noted in early diastole. It is significant that this considerably increased gradient occurred in association with a low cardiac index of 2.2 liters. The right ventricular pressure in early diastole dropped to low levels, while the right atrial pressure remained elevated. The pressure in the ventricle then rose gradually throughout diastole to approximate the atrial pressure level at end diastole. This is in contrast to the early diastolic dip and abrupt rise to high levels that are seen in tricuspid insufficiency.[11] After exercise in this patient there was an accentuation of this pattern with an atrioventricular pressure gradient of considerable magnitude in early diastole. A reduction in this gradient occurred following operative enlargement of the tricuspid valve orifice.

The resting pressure patterns in Cases 1 and 2 demonstrated an increased atrioventricular gradient at the end of diastole as a result of the prominent *a* waves. However, there was only a very small pressure gradient during early diastole. Exercise produced a high-amplitude tricuspid insufficiency wave in these patients, and subsequent findings showed no surgically significant tricuspid stenosis. It is, therefore, recommended that the increase in the early diastolic gradient is the most dependable hemodynamic characteristic of surgical tricuspid stenosis. Further hemodynamic studies with correlation at surgery will be necessary to determine the magnitude of this gradient indicating significant tricuspid stenosis.

Surgical Aspects of Tricuspid Stenosis.—These patients illustrate the severe degree of impairment of cardiac function produced by the multiple valve lesions that characteristically occur with tricuspid valve disease. The operative fatality in the first patient demonstrates the marked limitation of cardiac reserve in this situation.

A surgical fatality in a patient with tricuspid stenosis is also described by Ferrer and associates.[9] Cases 2 and 3 experienced complicated postoperative courses marked by increasing fluid retention, marked dyspnea, and severe chest pain. This syndrome suggested a reactivation of rheumatic fever as described by Soloff and associates.[13] The outlook of these patients without surgery is such that the ultimate results justify the high surgical risk. Case 2 has shown a remarkable improvement despite severe involvement of the mitral and tricuspid valves and moderate involvement of the aortic valve. Case 3 has been followed only a relatively short period since surgery but appears definitely improved.

A one-stage operative procedure is recommended using a wide transverse anterior thoracotomy permitting adequate exposure of both atria. Mitral commissurotomy is performed first in order to avoid engorgement of the pulmonary vascular bed that might occur secondary to a sudden increase in right ventricular output if the tricuspid valve orifice were dilated initially.

SUMMARY

The patients presented at this time demonstrate that the association of mitral stenosis with tricuspid valve disease represents an operable state. Thoughtful consideration of the history and careful physical examination will usually indicate the presence of tricuspid disease. Hemodynamic studies in such patients, with attention to the atrioventricular pressure gradient in early diastole, will aid in arriving at a decision regarding the operability of the tricuspid lesion. The operative mortality and morbidity are high in this type of patient but the probability of improvement warrants operative therapy.

CONCLUSIONS

1. Tricuspid and mitral commissurotomies were performed in one patient with good results.
2. Two patients with mitral stenosis and tricuspid insufficiency were operated upon with excellent results in one patient.
3. The clinical and physiologic studies are reviewed and criteria for the diagnosis of tricuspid stenosis presented.

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PULMONARY VALVULAR STENOSIS WITH INTACT VENTRICULAR SEPTUM: ISOLATED VALVULAR STENOSIS AND VALVULAR STENOSIS ASSOCIATED WITH INTERATRIAL SHUNT

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THE apparent rarity of congenital pulmonary valvular stenosis noted in the literature was based upon a study of post-mortem materials[1] and is not borne out by current clinical experience. The numerous recent reports and reviews of pulmonary valvular stenosis with and without a patent foramen ovale (or atrial septal defect) indicate the discrepancy between post-mortem and clinical incidence.[2-7] The true incidence of pulmonary valvular stenosis may be impossible to determine, but it is not a relatively rare abnormality; its recognition depends upon clinical and specialized laboratory techniques. Surgical correction of the lesion is possible.[8,9]

As a result of more intensive investigation of individuals with congenital cardiac abnormalities, it has become evident that many with pulmonary valvular stenosis are virtually symptom-free and are frequently erroneously believed to have one or more septal defects. The purpose of this paper is to point out the common occurrence of this abnormality, to classify the twenty-eight patients studied in this clinic according to the anatomic lesion, and to correlate signs and symptoms with objective findings.

Uncomplicated stenosis of the outflow tract of the right ventricle, pulmonary infundibular stenosis, not only is related to valvular stenosis embryologically but may be at times clinically and physiologically indistinguishable from it. However, in our laboratory we believe that it is possible to distinguish with near certainty between valvular and infundibular stenosis by specialized diagnostic procedures. Therefore, infundibular stenosis will not be discussed but will be treated in a separate publication.[10]

METHODS

These patients were admitted to the Childrens Hospital for specific cardiac study. Complete history, physical examination, blood and urine examination, electrocardiogram, and radiographic and fluoroscopic examination of the heart

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were done. Heart catheterization was done in the usual manner. Catheter lumen pressure, brachial artery pressure, and respiration were photographically recorded by appropriate strain gauges (Statham) with the simultaneous electrocardiogram. Exercise tests were not done; many of these subjects were young children requiring moderate sedation or basal anesthesia making coordinated exercise usually impossible.

Blood oxygen was determined manometrically by the technique of Van Slyke and Neil.[11] Oxygen consumption was measured by either use of the Pauling Oximeter and the wet-test meter or the closed spirometer. In some patients the oxygen consumption was determined by the routine basal metabolism equipment. Cardiac output was calculated by the Fick principle, and intracardiac shunts were computed by accepted methods.[12]

Angiocardiography was done with the Sanchez-Perez cassette changer; six 10 inch x 10 inch films were taken 0.7 sec. apart, usually timed so that the first exposure was taken with the dye column in the superior vena cava. Seventy per cent Diodrast was injected as rapidly as possible through the vein previously used in cardiac catheterization. Angiocardiography was not done in those individuals in whom a recurrent or persistent tachycardia occurred during catheterization or where dye sensitivity was shown to exist by prior intravenous testing with diluted Diodrast. To visualize most clearly the region of the pulmonary valve and the immediate postvalvular region, the procedure was usually done in the left lateral position.

RESULTS

The twenty-eight cases of pulmonary valvular stenosis are divided into two groups based upon the absence or presence of an atrial shunt: (1) isolated pulmonary valvular stenosis; (2) pulmonary valvular stenosis with patent foramen ovale or atrial septal defect.

In the following material the clinical, electrocardiographic, radiographic, cardiac catheterization, and angiocardiographic data will be given together for each group of patients and are presented in Tables I and II.

CLINICAL FINDINGS

Isolated Pulmonary Stenosis.—There were twelve patients (Table I) with isolated valvular stenosis; seven males and five females, ranging from 4 to 34 years of age. Easy fatigue was present in nine, and six complained of dyspnea on exertion. By history, cyanosis was absent and squatting was noted in only one child. On physical examination, cyanosis and clubbing were absent in all. One patient had been in right-heart failure and had a pulsating liver (G.H.). A systolic thrill was present in all but one patient, maximal in intensity at the left sternal border in the second and third intercostal spaces. An accompanying loud, rough, harsh Grade 4* systolic murmur was also present with maximal intensity in the same region; it was widely transmitted to the entire precordium,

*Grading of murmurs is on the scale of 1–4.

TABLE I. ISOLATED PULMONARY VALVULAR STENOSIS: CLINICAL AND LABORATORY DATA

CASE NO.	PATIENT	SEX	AGE (YR.)	HT. (IN.)	WT. (LB.)	SYMPTOMS			PHYSICAL FINDINGS							X-RAY					ECG	GROWTH STATUS (WETZEL GRID)	
												CARDIAC											
						EASY FATIGUE	EXERTIONAL DYSPNEA	SQUATTING	BLOOD PRESSURE	CYANOSIS	CLUBBING	THRILL	MURMUR		P_2	RT. ATRIUM ENLG'D	RT. VENTRICLE ENLG'D	PROMIN. PULMON. ARTERY SEGMENT	PULMONARY VASCULARITY	GRAMS HEMOGLOBIN	RT. VENTRICULAR HYPERTROPHY	CHANNEL	AUXODROME (%)
													SYSTOLIC	DIASTOLIC									
1	NS	F	6	44	40	0	0	0	116/80	0	0	0	+	0	D	+	+	+	D	13.9	+	M 32	67
2	EM	F	4	43	44	0	0	0	118/60	0	0	+	+	0	D	+	+	+	D	12.6	+	$A_3$40	10
3	FB	M	10	56	94	+	+		120/82	0	0	+	+	0	D	+	+	+	D	12.4	0	$A_3$120	2
4	JN	M	12	56	87	+	0	0	120/70	0	0	+	+	0	D	±	±	+	D	14.0	+	$B_1$113	17
5	GH	M	15½	62	97	+	+	0	88/70	0	0	+	+	0	D/A	+	+	+	D	16.0	+	$B_2$128	82
6	CR	F	12	61	99	+	+	0	110/70	0	0	+	+	0	D	+	+	+	D	15.6	+	M 128	10
7	GS	M	8½	52	71	+	0	0	103/56	0	0	+	+	+	N	+	+	+	D	13.4	+	M 91	15
8	EH	M	34	65	160	+	+	0	116/80	0	0	+	+	0	D	+	+	+	D	15.4	+		
9	OS	M	15	62	99	+	+		104/68	0	0	+	+	0	D	+	+	+	D	16.6	+	$B_1$130	85
10	RL	M	14	62	103	0	0	0	115/60	0	0	+	+	0	D	+	+	+	D	16.6	+	$B_1$133	65
11	MN	F	10½	53	75	+	+	0	100/65	0	0	+	+	0	D	+	+	+	D	13.9	+	$A_2$97	15
12	SK	F	7½	49	63	+	0	0	122/66	0	0	+	+	0	N	N	+	+	D	13.5	0	$A_3$77	10

TABLE I. ISOLATED PULMONARY VALVULAR STENOSIS: CLINICAL AND LABORATORY DATA (CONTINUED)

	ANGIOCARDIOGRAM					CARDIAC CATHETERIZATION						HEMODYNAMICS									
													PER CENT OXYGEN SATURATION								
CASE NO.	INCREASED TRANSIT TIME	POSTSTENOTIC DILATATION	EARLY FILL LEFT ATRIUM	EARLY FILL LEFT VENTRICLE	EARLY FILL AORTA	VENTURI CURVE	ARTERIAL OXYGEN SATURATION	PULMONARY ARTERIAL PRESSURE	RIGHT VENTRICLE PRESSURE	RIGHT ATRIAL PRESSURE	INTRA-ARTERIAL PRESSURE	OXYGEN CAPACITY (C.C./L.)	CAVAL	RIGHT ATRIUM	RIGHT VENTRICLE	PULMONARY ARTERY	O_2 CONSUMPTION (C.C./MIN.)	SURFACE AREA (M^2)	PULMONARY BLOOD FLOW (L./MIN.)	SYSTEMIC BLOOD FLOW (L./MIN.)	CARDIAC INDEX (L./M^2/MIN.)
1	+	+	0	0	0	+	92	27/10	62/–2	6/4	114/67	164	68	66	67	69	130	0.85	3.3	3.3	4.8
2					0	+	93	16/12	95/4	8/3	106/72	159	65	65	69	69	163	0.78	4.0	4.0	5.2
3	+	+	0	0	0	+	94	17/11	50/4	7/4	104/54	169		70	76	76	134	1.3	3.7	3.7	2.9
4	+	+	0	0	0	+	97	20/7	188/5	22/11	116/65	168		76	80	79	208	1.4	6.8	6.8	4.8
5	+	0	0	0	0	+	97	15/5	260/0	15/0	110/72	192	51	55	54	53	245	1.4	2.9	2.9	2.0
6	+	+	0	0	0	+	94	8/–2	122/3	12/4	112/84	163		65	65	61	174	1.4	3.4	3.4	2.4
7	+	+	0	0	0	+	97	15/1	64/1	22/6	103/56	168	70	72	72	76	181	1.1	5.4	5.4	5.2
8						+	93	29/10	155/4	17/4	115/100	206	56	58	59	60	330	1.8	4.5	4.5	2.5
9	+	+	0	0	0	+	93	12/2	152/0	8/3	138/78	180	51	52	52	50	206	1.42	2.55	2.55	1.8
10	+	+	+	0	0	+	91	16/8	181/0	6/2	116/65	183	71	70	71	70	191	1.44	5.0	5.0	3.47
11	+	+	0	0	0	+	94	15/9	104/–1	5/2	128/78	188	64	69	73	75	155	1.12	3.9	3.9	3.5
12	+	+	0	0	0	0	97	22/13	73/3	12/5	122/66	167	64	69	73	73	127	1.0	3.17	3.17	3.17

0 = the specific symptom or abnormal finding under consideration is absent; D = diminished; D/A = diminished to absent; A = absent; I = increased. + = finding is present without reference to the degree or severity.

left axilla, back, and neck. A short diastolic murmur in the pulmonic area was described in one individual. The intensity of the pulmonary second sound was decreased or absent in ten patients and normal in two. Hemoglobin concentration was not elevated in any of these patients, averaging 14.4 grams. Growth and development plotted on the Wetzel grid revealed four to be superior or above the 67 per cent auxodrome, while only two were below this level, falling on the 85 per cent and 82 per cent auxodrome. The latter individual was the one whose clinical course was complicated by a pulsating liver and cardiac failure.

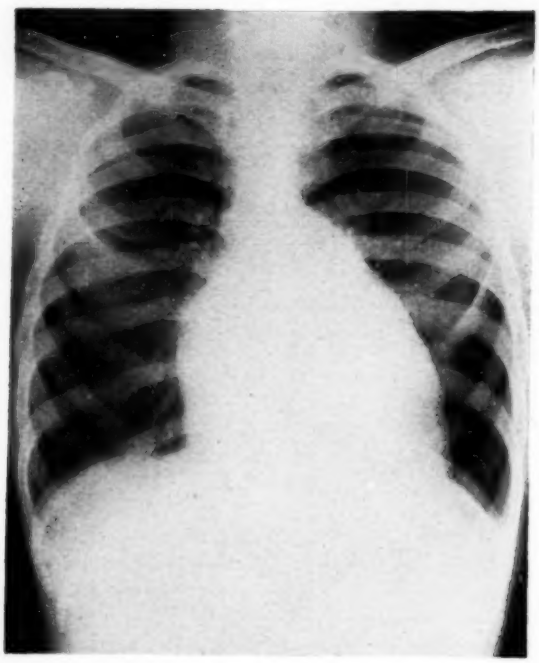

Fig. 1.—Isolated pulmonary valvular stenosis. G. H. (No. 5). The under vascularized lungs are in striking contrast to the large heart. The prominent pulmonary artery segment formed by the poststenotic dilatation of the pulmonary artery is obscured by the large right ventricular mass.

The electrocardiogram revealed evidence of right ventricular hypertrophy in ten of the twelve patients. One child with a normal electrocardiogram (F.B.) had a right ventricular systolic pressure of 50 mm. Hg which was the lowest ventricular systolic pressure in the group. The right ventricular pressure in the other patient (S.K.) was 73 mm. Hg. By roentgenographic examination all patients had abnormal-sized hearts. In all there were enlargement of the right ventricle, prominence of the pulmonary artery segment, and diminished vascularity in the distal lung fields (Fig. 1).

The angiocardiogram showed slow filling and emptying of the pulmonary vessels and in all but one individual there was a demonstrable filling defect between the outflow tract of the right ventricle and pulmonary artery (Fig. 2). Poststenotic dilatation of the pulmonary artery was present in all instances.

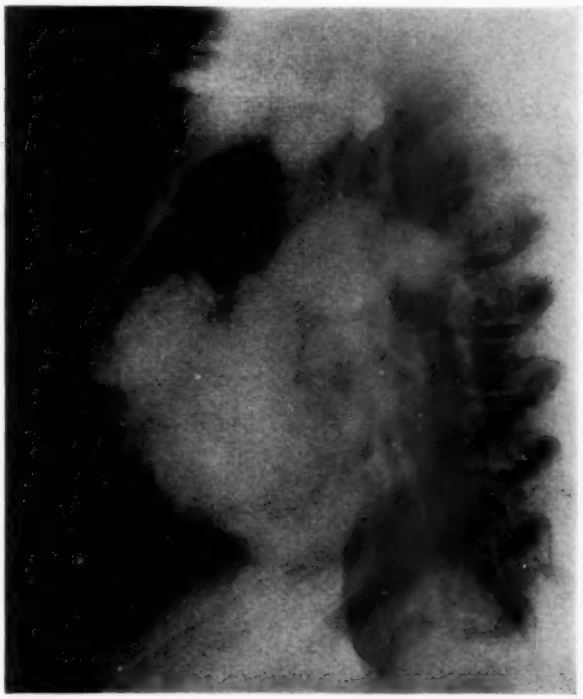

Fig. 2.—Isolated pulmonary valvular stenosis. G. H. (No. 5). Dye column has passed through the right heart and is in the pulmonary artery and its branches. The region of poststenotic dilatation is quite prominent. The left pulmonary artery continues posteriorly and is dilated, while the right is quite small and is seen descending to the right.

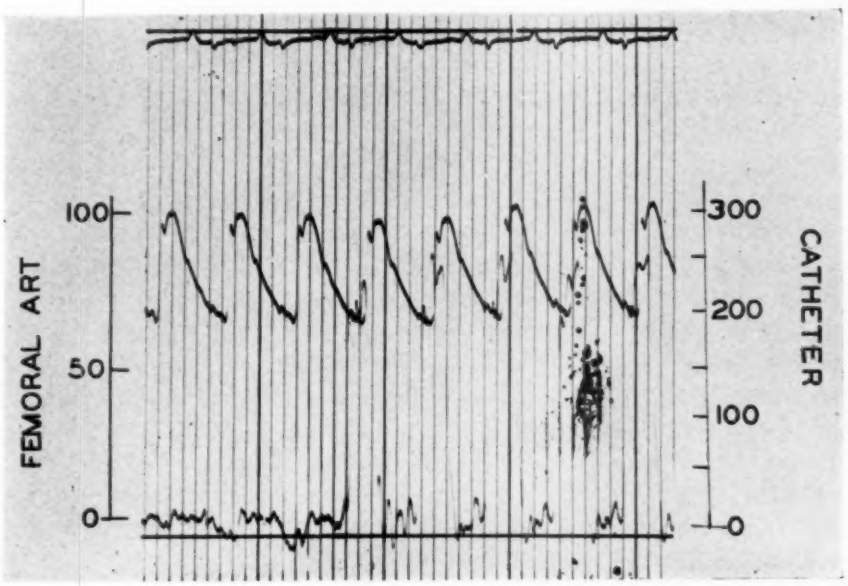

Fig. 3.—Isolated pulmonary valvular stenosis. G. H. (No. 5). The pressure tracing was recorded during withdrawal of the catheter from the main pulmonary artery into the right ventricle immediately below the pulmonary valve. The initial downward deflection of the catheter tracing occurs approximately 0.04 sec. after the initial deflection of the QRS of the electrocardiogram.

Cardiac catheterization in all instances demonstrated a differential pressure at the pulmonary valve, with normal or low pressure in the pulmonary artery, and high pressure in the right ventricle. The region of the pressure change was extremely narrow, indicating a precise localized region of pulmonary obstruction (Fig. 3). In the region of the stenosis, the high-ejection velocity produced "negative" pressure or Venturi curves. These could be identified in most of the tracings.[13] Systolic pressure in the right ventricle ranged from 50 mm. Hg to 260 mm. Hg, and in six of the twelve individuals was in excess of the arterial blood pressure. Atrial pressure was elevated in six of the twelve patients. Arterial oxygen saturation was normal, and cardiac output in the resting state was within normal limits in all.

Pulmonary Valvular Stenosis With Atrial Septal Defect or Patent Foramen Ovale.—Sixteen patients (Table II), ten males and six females, fell into this category, ranging in age from 4 to 13 years: 68 per cent complained of easy fatigue and exertional dyspnea; 50 per cent gave a history of some cyanosis on exertion beginning at birth, with 8 years as the maximum duration of cyanosis in one patient. In only five did cyanosis become constant with accompanying clubbing of fingers and toes. One individual gave a history of squatting when tired. Eleven patients had a systolic thrill with the point of maximal intensity varying from the second to fourth left intercostal spaces at the left costal margin. All patients had a loud, rough and harsh, Grade 4 systolic murmur with maximal intensity in the second to fourth left intercostal spaces. The murmur was widely transmitted over the entire precordium, left axilla, posterior thorax, and into the neck. In one patient a faint diastolic murmur was described over the pulmonary area. The pulmonic second sound was decreased or absent in thirteen but increased in three patients. In six the hemoglobin concentration was greater than 16 grams. Plotted on the Wetzel grid, only two patients fell below the 67 per cent (median) auxodrome. The electrocardiogram demonstrated right ventricular hypertrophy in all cases.

All sixteen patients had radiographic evidence of cardiac enlargement, termed "slight to moderate," with enlargement of the right atrium and right ventricle (Fig. 4). The left atrium was not enlarged in any patient. The pulmonary artery segment was prominent in all, and distal pulmonary vascularity was decreased in fifteen of the sixteen, only one child showing increased vascularity in the distal lung fields.

Angiocardiography was done in twelve patients and in each instance demonstrated slow filling and emptying of the pulmonary arteries. In eleven of the twelve patients (91 per cent), a filling defect could be demonstrated between the outflow tract of the right ventricle and the pulmonary artery. Poststenotic dilatation of the pulmonary artery was present in eleven patients. Four patients demonstrated early filling of the left atrium following filling of the right atrium (Fig. 5). Premature opacification of the aorta was not present in any of the twelve subjects.

Cardiac catheterization demonstrated a zone of valvular stenosis in all individuals, with a normal or low pressure in the pulmonary artery and elevated

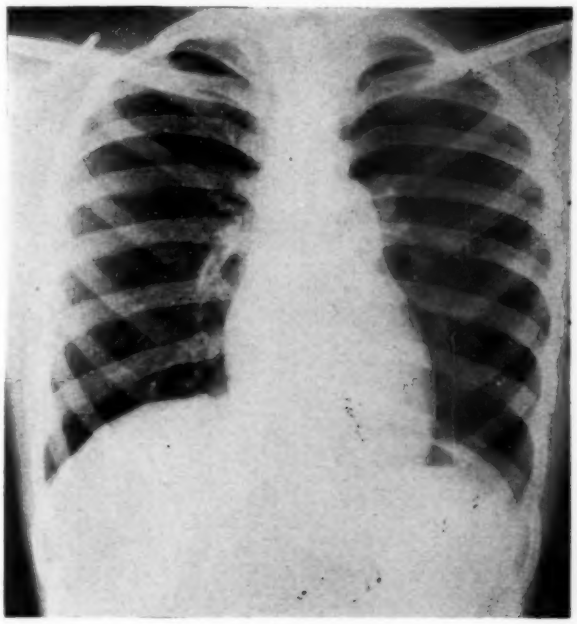

Fig. 4.—Pulmonary valvular stenosis with atrial septal defect. J. C. (No. 21). The heart is only slightly enlarged and the region of the poststenotic dilatation is readily seen in the left upper cardiac shadow.

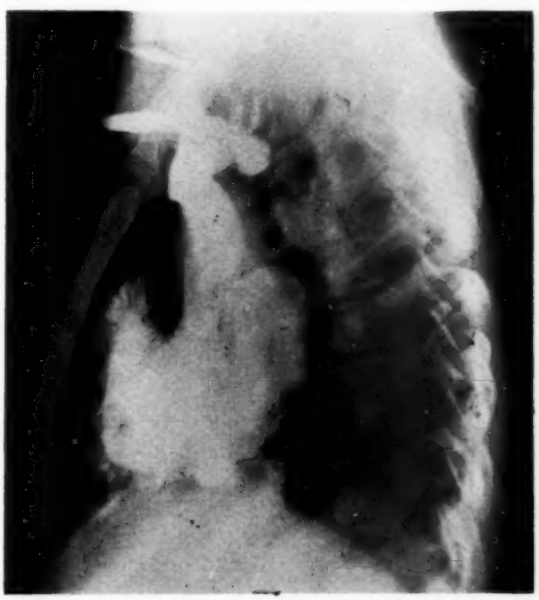

Fig. 5.—Pulmonary valvular stenosis with atrial septal defect. J. C. (No. 21). Premature opacification of the left atrium is seen in the posterior upper cardiac shadow. The zone of poststenotic dilatation is apparent but not well shown. This film was selected primarily to illustrate the early filling of the left atrium.

TABLE II. PULMONARY VALVULAR STENOSIS WITH ATRIAL SEPTAL DEFECT OR PATENT FORAMEN OVALE: CLINICAL AND LABORATORY DATA

CASE NO.	PATIENT	SEX	AGE (YR.)	HT. (IN.)	WT. (LB.)	SYMPTOMS			PHYSICAL FINDINGS							X-RAY				GRAMS HEMOGLOBIN	ECG	GROWTH STATUS (WETZEL GRID)	
												CARDIAC											
													MURMUR										
						EASY FATIGUE	EXERTIONAL DYSPNEA	SQUATTING	BLOOD PRESSURE	CYANOSIS	CLUBBING	THRILL	SYS-STOLIC	DIAS-TOLIC	P_2	RT. ATRIUM ENLG'D	RT. VENTRICLE ENLG'D	PROMIN. PULMON. ARTERY SEGMENT	PULMONARY VASCULARITY		RT. VENTRICULAR HYPERTROPHY	CHANNEL	AUXODROME (%)
13	RB	F	12	61	95	0	0	0	118/70	0	0	+	+	0	D	+	+	+	D	13.1	+	$B_1$124	10
14	ER	F	12	61	114	+	+	+	90/50	0	0	0	+	0	D	+	+	+	D	12.4	+	$A_2$141	5
15	CF	M	11	64	123	+	+	0	100/55	0	0	+	+	0	D	+	+	+	D	17.4	+	M 135	15
16	BC	M	11	59	97	0	0	0	97/56	0	0	+	+	+	D	+	+	+	D	16.3	+	M 125	8
17	AW	M	5½	45	43	+	+	0	100/78	0	0	+	+	0	D	+	+	+	D	15.0	+	M 47	70
18	RO	M	13	51	97	+	+	0	112/72	+	+	0	+	0	D	+	+	+	D	19.0	+	$B_2$118	10
19	MC	M	11		86	+	+	0	104/67	+	+	0	+	0	D	+	+	+	D	17.4	+	M 112	15
20	JF	M	10	53	54	+	+	0	104/60	+	+	+	+	0	D	0	0	+	D	15 0	+	$B_1$78	75
21	JC	F	12	58	85	+	+	0	95/75	+	+	+	+	0	D	0	+	+	D	21.6	+	$B_1$110	30
22	ES	M	4	38	34	+	+	0	88/52	0	0	+	+	0	D	+	+	I	D	12.3	+	$A_3$15	50
23	DS	M	5½	40	37	+	+	0	95/50	±	0	+	+	0	A	+	+	I	D	13.5	+	$A_3$22	60
24	MM	F	5	41	32	0	0	0	120/80	0	0	0	+	0	I	+	+	I	I	12.9	+	M 7	67
25	SS	F	5½	46	46	+	+	0	100/80	±	0	+	+	0	D	0	+	I	D	15.6	+	M 45	10
26	DH	M	12½	59	83	0	0	0	104/76	0	0	0	+	0	I	+	+	I	I	14.9	+	$B_1$109	67
27	CC	F	6½	48	46	+	+	0	92/60	±	0	+	+	0	D	+	+	I	D	14.6	+	$B_2$47	20
28	SC	M	6	45	39	0	+	0	94/68	+	0	+	+	0	I	+	+	I	D	18.0	+	$B_2$30	67

TABLE II. PULMONARY VALVULAR STENOSIS WITH ATRIAL SEPTAL DEFECT OR PATENT FORAMEN OVALE: CLINICAL AND LABORATORY DATA (CONTINUED)

TABLE II. PULMONARY VALVULAR STENOSIS WITH ATRIAL SEPTAL DEFECT OR PATENT FORAMEN OVALE: CLINICAL AND LABORATORY DATA (CONTINUED)

CASE NO.	ANGIOCARDIOGRAM					CARDIAC CATHETERIZATION								HEMODYNAMICS											
	INCREASED TRANSIT TIME	POSTSTENOTIC DILATATION	EARLY FILL LEFT ATRIUM	EARLY FILL LEFT VENTRICLE	EARLY FILL AORTA	VENTURI CURVE	CATHETER THROUGH DEFECT	ARTERIAL OXYGEN SATURATION	PULMONARY ARTERIAL PRESSURE	RIGHT VENTRICLE PRESSURE	RIGHT ATRIAL PRESSURE	INTRA-ARTERIAL PRESSURE	LEFT ATRIAL PRESSURE	OXYGEN CAPACITY (C.C./L.)	PER CENT OXYGEN SATURATION				O_2 CONSUMPTION (C.C./MIN.)	SURFACE AREA (M^2)	PULMONARY BLOOD FLOW (L./MIN.)	SYSTEMIC BLOOD FLOW (L./MIN.)	RIGHT-TO-LEFT SHUNT	LEFT-TO-RIGHT SHUNT	CARDIAC INDEX
															CAVAL	RIGHT ATRIUM	RIGHT VENTRICLE	PULMONARY ARTERY							
13	+	+	0	0	0	+	0		12/9	62/2	21/11			177		65	64	67							
14						+	0	85	20/12	79/2	12/8	113/68		171		61	57	61	179	1.5	3.0	4.3	1.3	0	2.87
15	+	+				+	0	88	13/7	76/–8	10/–2	100/55		227	73	81	82	84	163	1.42	6.12	5.85	2.31	2.58	4.1
16	+	+	0	0	0	+	0	90	23/5	92/0	8/3	97/56		215	69	65	66	69	185	1.38	3.14	3.8	0.9	0.24	2.75
17	+	+	0	0	0	+	0	88	34/9	204/5	25/7	98/48		179	57	57	57	55	156	0.8	2.13	2.65	2.65	0.52	3.3
18						+		80	15/10	117/5	23/13	112/72		243	58	74	72	73	268	1.4	4.77	7.2	3.63	1.2	5.14
19	+	?	0	0	0	+	0	82	13/7	162/–4	9/–1	104/67		232	59	60	58	58	200		2.23	3.6	1.37	0	
20	+	+	+	+	0	+	+	81	18/9	120/8	21/7	142/84	18/11	197		60	60	61	169	1.0	2.5	4.4	1.9	0	4.4
21	+	+	+	+	0	+	+	80	21/16	127/10	14/4	108/63	14/4	264	63	63	64	64	170	1.28	1.8	4.1	2.3	0	3.2
22	+	+	+	0	0	+	+	95	22/17	153/5	12/4	92/65		156	63	62	60	54	110	0.68	2.15	2.15	0	0	3.16
23	+	+	+	0	0	0	+	88	25/19	106/6	17	110/60		168	64	66	67	72	105	0.69	2.56	2.78	0.76	0.53	4.05
24	+	+	0	0	0	0	0	86	20/6	59/0	6/2	112/70		153	64	72	67	68	95	0.78	2.1	2.86	0.9	0.38	3.76
25	+	+	0	0	0	+	+	72	22/9	136/3	11	82/44	8	190	62	62	62	64	102	0.78	1.51	4.44	2.93	0	5.7
26	+	+	0	0	0	+		95	36/19	70/–1	7	123/77	*												
27						+	+	86	20/15	143/6	13/6	110/50	**	172	54	59	56	61	142	0.86	2.36	2.62	0.62	.36	3.05
28	+	+	+	0	0	+	0	74	19/11	173/5	13/6	102/56		217	51	48	45	41	156	0.76	1.44	2.52	1.08	0	3.3

See Table I for key. * = D.H. showed scattered high oxygen saturation values in the right side of the heart and pulmonary artery, and in retrospect may have a marked left-to-right interatrial shunt resulting in relative pulmonary stenosis. He is to be studied again.

** = In C.C. the catheter passed into the left atrium during manipulation and accidentally slipped out. It was not possible to direct it back into this chamber for further samples and pressures.

right ventricular systolic pressure which in ten patients was above 100 mm. Hg, and in four above 150 mm. Hg (Fig. 6). In seven of the twelve patients, right ventricular pressure exceeded the simultaneously recorded arterial pressure. Resting arterial oxygen saturation varied between normal and 72 per cent and could not be related to the degree of right ventricular hypertension. The resting cardiac output was normal or minimally diminished. The cardiac catheter passed from the right to the left atrium in seven patients, and in six of these at least moderate arterial unsaturation was present. Three of the four patients with angiocardiographic evidence of right-to-left interatrial flow had arterial unsaturation. In the remainder of this group the absence of premature visualization of the aorta by angiocardiography, comparison of right-heart blood-oxygen values, and arterial unsaturation permitted the diagnosis of an interatrial shunt.

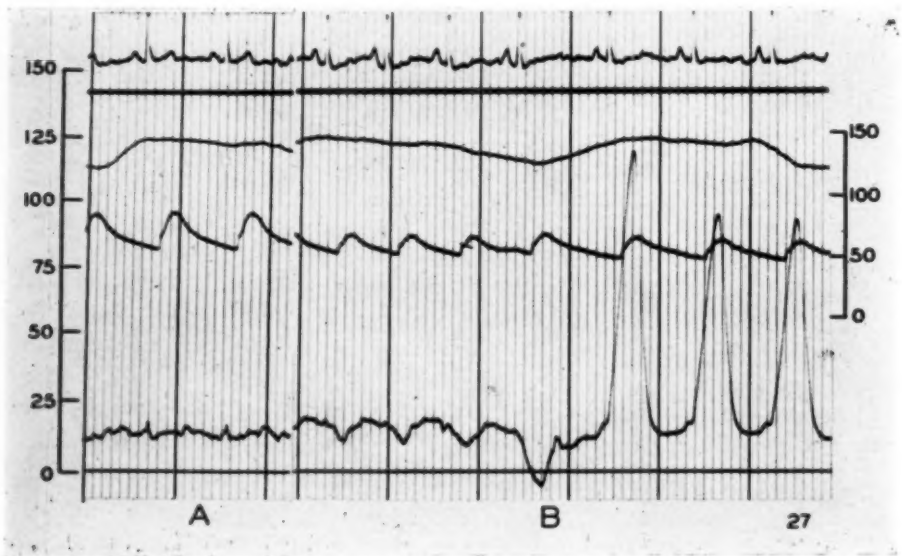

Fig. 6.—Pulmonary valvular stenosis with atrial septal defect. J. C. (No. 21). The pressure tracings are damped. They are shown to indicate the positive pressure deflection in the right pulmonary artery (*A*), the "negative" pressure tracing of the main pulmonary artery (*B*), and the high right ventricular pressure below the pulmonary valve (*B*).

DISCUSSION

Isolated Pulmonary Valvular Stenosis With Intact Septa.—Increased ease of fatigue was the first and outstanding symptom of this group, occurring in nine of the twelve cases, in all ages (4 to 34 years) and increasing progressively in severity with age. Cyanosis, squatting, or clubbing were not present, and polycythemia was absent. As might be anticipated, with intact septa the arterial oxygen saturation was normal. The generally excellent physical development of these children was noteworthy. Only two individuals failed to come up to or exceed the median position on the Wetzel grid, one of whom was severely incapacitated (O. S.) while the other had severe right heart failure (G. H.). This

is in marked contrast to the usual child with the Tetralogy of Fallot where retardation of physical growth and development is the rule. This single finding indicates the usual adequacy of peripheral tissue oxygenation to allow for normal growth and development, at least during the early years.

A thrill and loud, rough systolic murmur were constantly present in each case, with maximal intensity over the pulmonic area and wide transmission of the murmur to the thorax, shoulders, and neck. Decreased intensity of the pulmonary second sound was noted in all but two patients. The character and location of the thrill and murmur were in themselves highly suggestive of pulmonary valvular stenosis. In the typical situation we did not believe that there was any difficulty in clinical differentiation between pulmonary valvular stenosis and ventricular septal defect.

Fluoroscopic and radiographic examination of the chest in each instance showed right ventricular and right atrial enlargement (eleven of twelve patients) and large main and left hilar pulmonary arteries. Peripheral pulmonary vascularity was decreased in each instance. The angiocardiogram demonstrated slow filling and emptying of the pulmonary arteries, and in four patients of this group the site of stenosis could be localized by the filling defect between the outflow tract of the right ventricle and the pulmonary artery.

Pulmonary Valvular Stenosis With Patent Foramen Ovale Or Atrial Septal Defect.—The sixteen patients in this group included four who were entirely asymptomatic (No. 13, 16, 24, and 26). These four children presented a clinical picture indistinguishable from that seen in pure pulmonary stenosis of mild degree. The general physical development was better than average in two of the four. A prominent thrill and Grade 4 systolic murmur were present with maximum intensity over the pulmonic area, and the pulmonic second sound was decreased. By x-ray, cardiac enlargement was present but minimal in all four, although the pulmonary artery segment was prominent, pulmonary vascularity was decreased, and the right ventricle enlarged. The angiocardiogram showed the typical slow filling and emptying of the pulmonary arteries and a filling defect between the outflow tract of the right ventricle and pulmonary artery. The right atrial pressures were lower than in other cases of this group despite hypertension in the right ventricle, and right ventricular pressure was below 100 mm. Hg in all four, and below 75 mm. Hg in three.

These four asymptomatic patients represent an interesting transition group between those with isolated pulmonary stenosis, without cyanosis, and those with the additional lesion of atrial septal defect or patent foramen ovale, with cyanosis. Here the valvular stenosis was not so severe as to cause marked right ventricular hypertension, and the right atrial pressure was generally normal. The lack of cyanosis is understandable as is the absence of dyspnea and of exercise fatigue.

These four patients were under 14 years of age. It is possible that with increasing age cyanosis will occur as the pulmonary stenosis becomes relatively more severe and pressures in the right ventricle and atrium become increasingly elevated with the resulting development of a significant right-to-left interatrial shunt.

The remaining twelve patients presented an almost constant clinical picture. Each complained of easy fatigue and exertional dyspnea as the outstanding symptoms. Cyanosis was apparent only with exercise in three patients, but in five it was constant. Occasional squatting was noted in only one case. In the Wetzel grid evaluation of growth and development, the auxodrome status fell below the 67 per cent median in two patients. The prominent systolic thrill in the pulmonic area was constantly accompanied by a loud Grade 3 to Grade 4 harsh, rough systolic murmur which was widely transmitted to the entire precordium, neck and back. The pulmonic second sound was decreased or absent in each. Precordial bulging was noted in the four patients with the greatest cardiothoracic ratios of 0.59 to 0.70. Laboratory data showed a minimal hemoglobin level of 15 grams and 5.7 million red blood cells in seven patients. In only one was the hemoglobin concentration below normal (12.8 grams). The electrocardiogram constantly demonstrated right ventricular hypertrophy. The radiographic and fluoroscopic characteristics were essentially the same as described in patients with isolated pulmonary valvular stenosis. The findings by angiocardiography were identical to those noted in isolated valvular stenosis, with the additional feature of successive visualization of the left atrium and often the left ventricle and aorta.

CONSIDERATION OF SPECIFIC FINDINGS IN PULMONARY VALVULAR STENOSIS

Dow and associates[4] have correlated in a comprehensive review the pathologic anatomy and physiologic alterations in pulmonary stenosis. We are in agreement with their findings but in addition would like to emphasize and clarify certain points.

The stenotic pulmonary valve forces the right ventricle to work against an increased resistance, ultimately leading to right ventricular hypertension and myocardial hypertrophy. This may result in increased tension in the atrium, with enlargement, giving rise to the "Pulmonale P wave" in the electrocardiogram and "giant" auricular pressure waves found in catheterization of the right side of the heart when the interatrial septum is intact.[14] The increased and relatively fixed or constant resistance to outflow from the right ventricle at the valve is the common denominator to the anatomic and physiologic alterations in pulmonary valvular stenosis. The lumen of the stenotic pulmonary valve has been postulated to increase relatively little during growth, and with increasing age and needs resulting from growth the pulmonary circulation (and total circulation) gradually becomes relatively more deficient. During exertion with an accompanying demand for increased cardiac output, the limiting stenotic orifice becomes manifest by fatigue and/or exertional dyspnea. The fact that resting cardiac output in these patients is often not only normal but is still capable of limited further increase with exertion[4,15] is a tribute to the often underrated high pressure potentialities of the right ventricle.

The Physical Examination.—The physical findings are strikingly similar in almost all patients, with uniformity of opinion among various observers.[2-6,15] The differences in findings are only of degree and are undoubtedly due to age dif-

ference in patients, variations in the degree of pulmonary valvular stenosis as reflected in the right ventricular pressure, and possible different criteria in the cardiac examination.

We have been impressed by the apparent ease with which the aortic second sound may be mistaken for the pulmonary second sound, especially in the sitting position. It has been suggested by others[16] that the occasionally noted increased intensity of the pulmonary second sound in pulmonary stenosis is due to hearing the aortic second sound in the "pulmonary area" and we concur in this view. The difference in pitch between the aortic second sound and pulmonary second, especially in pulmonary stenosis, should allow easier distinction between them. This may be difficult in the sitting position, but in recumbency this differentiation is simpler.

A diastolic murmur is described in two of our patients. This has been noted by a number of observers,[4,16] specifically excluded by others,[5] and not mentioned by still others.[6,15] Despite the apparent identification of a pulmonary diastolic murmur indicating insufficiency in our series and in the literature, it is difficult to understand how any significant reflux or regurgitation can occur under the existing anatomic circumstances of pulmonary valvular stenosis. We feel that such a diastolic "insufficiency" murmur is more probably the trailing end of the systolic murmur which could not be completely timed as systolic due to absence of a pulmonary second sound. Stethocardiograms are necessary for positive identification of the diastolic murmur and unfortunately such tracings have not been obtained.

The Electrocardiogram.—The most constant electrocardiographic pattern in pulmonary valvular stenosis is right ventricular hypertrophy, and the criteria are now too well recognized to need further definition.[17] Right-axis deviation alone, unless extreme, is not valid proof of right ventricular hypertrophy. The high percentage of our patients with right ventricular hypertrophy may be due to somewhat greater attention to techniques in obtaining the electrocardiogram[18] as well as the higher percentage of patients with very high right ventricular pressure. It has been a not infrequent experience that an electrocardiogram taken on the outside previous to the hospitalization for diagnostic study has failed to demonstrate right ventricular hypertrophy while the electrocardiogram taken during hospitalization has shown this abnormality. We have not noted any direct correlation between the degree of right ventricular hypertrophy and right ventricular pressure.

Roentgenologic Considerations.—The radiographic and fluoroscopic appearance of the heart vessels in pulmonary valvular stenosis have been well documented.[4,19] Humphrey[20] has defined more precisely the roentgen alterations in pulmonary valvular stenosis which have been extremely accurate in predicting the presence of this lesion. There is constant, but variable in degree, enlargement of the right ventricle, often enlargement of the right atrium, and dilation of the main pulmonary artery with rather marked dilation of the left pulmonary artery, and a normal or underdeveloped right pulmonary artery. Fluoroscopic examination shows the pulsations over the left hilar and main pulmonary artery

to be normal or somewhat increased while those in the right hilar pulmonary artery are diminished. Peripheral pulmonary vascularity is decreased, indicating decreased pulmonary blood flow. Fluoroscopy of the lung parenchyma is usually unsatisfactory for evaluation of vascularity, and careful radiographic examination is the only basis for unbiased opinion. It should be pointed out that often the prominent main and left hilar pulmonary arteries ("poststenotic dilatation") are misinterpreted as indicating normal vascularity. Conversely, it is this discrepancy between the appearance of these larger vessels and the undervascularized lung parenchyma that constitutes the striking appearance of the chest x-ray in typical isolated pulmonary valvular stenosis.

The Angiocardiogram.—Intravenous angiocardiography in patients with pulmonary valvular stenosis has not been attendant with the anticipated danger.[21] We use the procedure whenever the diagnosis of pulmonary valvular stenosis is suspected or known from either the clinical data or prior heart catheterization. The typical diagnostic angiocardiogram shows slow filling and emptying of the pulmonary arteries, persistent visualization of the right ventricle (increased transit time), thickened right ventricular wall, dilatation of the main and left hilar pulmonary arteries, a small right hilar pulmonary artery, and a filling defect at the pulmonary valve. In rare instances, the thin streaming jet of dye can be seen passing through the stenotic valve. The presence of an interatrial shunt permits early opacification of the left atrium, followed by visualization of the left ventricle and aorta, which is in contrast with the findings in Tetralogy of Fallot where premature opacification of the aorta is the rule. It is uncommon to find all the features of the angiocardiogram in older individuals, but in children they occur commonly. The anatomic demonstration of the heart chambers and vessels by contrast media gives supplemental data which cannot be ignored in the clinical evaluation of the patient.

Right-Heart Catheterization.—The demonstration of a sharply demarcated differential pressure zone at the pulmonary valve with a low or normal pressure in the pulmonary artery is the necessary physiologic proof of pulmonary valvular stenosis. Conversion of the great potential energy of the (hypertensive) right ventricle into velocity energy as fluid is pushed through the small orifice of the stenotic valve results in "negative pressure waves" when the catheter tip is in the valve (Venturi curves[13]). These curves have been an almost invariable finding in valvular stenosis.

In the presence of an interatrial communication the catheter may purposely or fortuitously pass from the right to left atrium and into pulmonary veins or through mitral valve orifice into the inflow tract of the left ventricle. Pressure curves, oxygen saturation, and catheter position are diagnostic features.

In our experience distinct differences in the cardiac catheterization data serve to distinguish isolated pulmonary valvular stenosis from the varying types of stenosis of the outflow tract (subvalvular ridge or diffuse infundibular stenosis with and without a subvalvular pocket) alone, or in combination with the valvular stenosis. The catheter "artifact" in the pressure tracing too often is an omnibus which holds the different significant pressure tracing patterns of these various

anatomic lesions. The importance of the different patterns of Venturi phenomena cannot be overlooked.[10] The position of the catheter tip indicating the stenotic site and its extent at fluoroscopy must be carefully correlated with the catheter tracing on the monitor cathrode-ray screen.

SUMMARY

1. Wide-spread application of cardiac catheterization in more accurate definition of congenital heart disease has dispelled the concept of rarity of isolated pulmonary valvular stenosis.

2. Clinical recognition may be fairly easy in the more severe cases. The characteristic clinical features are increasing exertional dyspnea and fatigue with increasing age, normal physical growth and development except where cyanosis is evident, marked systolic thrill and murmur maximal in the second and third left intercostal spaces and decreased or absent pulmonary second sound. Cyanosis is absent when an interatrial shunt is not present.

3. The shunting of blood from right to left through an atrial defect or patent foramen ovale results in slight to severe cyanosis which varies with the amount of shunted blood. These individuals usually are more restricted, and growth and physical impairment are common.

4. When the pulmonary valvular stenosis is less severe, the clinical diagnosis may be more difficult due to absence of fatigue and dyspnea, and great exercise tolerance and physical vigor may be prominent. In these instances the thrill and murmur may not be characteristic and a "septal defect" may be suspected.

5. The anatomic and physiologic alterations can be precicted from the high resistance of the pulmonary valve, and considered in this light, the increasing right ventricular hypertrophy expresses itself in the electrocardiographic, x-ray, and fluoroscopic configuration of the heart, and in catheterization and in angiocardiographic findings.

6. Despite a high degree of clinical suspicion and recognition of this congenital anomaly, we believe it is not possible to differentiate by clinical means among some of the varieties of subvalvular stenosis. Therefore, venous catheterization of the heart and angiocardiography should be utilized whenever possible. Cardiac catheterization characteristically shows a low pressure in the pulmonary artery and a higher pressure in the right ventricle which is proportional to the degree of valvular stenosis. Meticulous exploration of the region of stenosis will characteristically show an increasing negative pressure as the catheter is withdrawn from the pulmonary artery into the stream of the valve orifice (Venturi curves) and an abrupt change to the high pressure of the right ventricle.

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OBSERVATIONS ON THYROID FUNCTION IN HYPERTENSIVE PATIENTS TREATED WITH POTASSIUM THIOCYANATE

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THIOCYANATE has been used for many years in the treatment of hypertension, and it has been shown by various authors[1-4] that the drug has a definite pharmacologic depressor effect on the blood pressure. The mode of this action has not been clearly determined. It is usually stated that it acts as a sedative, or as a smooth muscle depressant, thereby causing vasodilatation. In a recent review, Thomas[4] indicates that its action may be hormonal, mediated through either the thyroid or adrenal glands.

Thyroid function in untreated essential hypertension is normal.[5] During thiocyanate therapy however, thyroid function may be depressed, even to myxedematous levels.[6-8] Although clinical hypothyroidism has been reported as a complication of thiocyanate treatment of hypertension, it does not appear to occur frequently. Taylor[9] noted hypothyroidism in only two of 100 patients treated; Barker and associates[6] observed eleven cases of thyroid enlargement in 246 persons treated.

It has repeatedly been shown with short-term, relatively acute experiments that thiocyanate can bring about a profound derangement of thyroid function.[10-12] The drug in some manner competes with, and thus inhibits, the uptake of circulating iodide by the thyroid gland. This block of iodide uptake is maintained only in the presence of adequate plasma levels of thiocyanate. After withdrawal of the drug and a rapid fall in plasma level, there is an immediate release of the inhibition of thyroid iodide uptake.[11]

There have been few observations regarding the effect on thyroid function of prolonged treatment of hypertensives with thiocyanates.[8,13] In their study of a group of hypertensive patients who had developed myxedema as a result of long-term treatment with potassium thiocyanate, Blackburn and associates[13] showed that there was a marked depression of the ability of the gland to take up radioiodine (I^{131}), a very low protein-bound plasma iodine level (PBI), and a depression of the basal metabolic rate. All of these reverted to normal values following discontinuation of the therapy. The present report deals with similar observations on a small group of hypertensive patients treated with conventional therapeutic doses of potassium thiocyanate (KSCN) over periods ranging from 6 to 52 or more weeks.

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METHOD

None of the subjects of this investigation had any demonstrable thyroid dysfunction judged on purely clinical grounds. As indices of thyroid function, the protein-bound plasma iodine concentration[14] and the twenty-four hour thyroid uptake of radioiodine[15] were used.

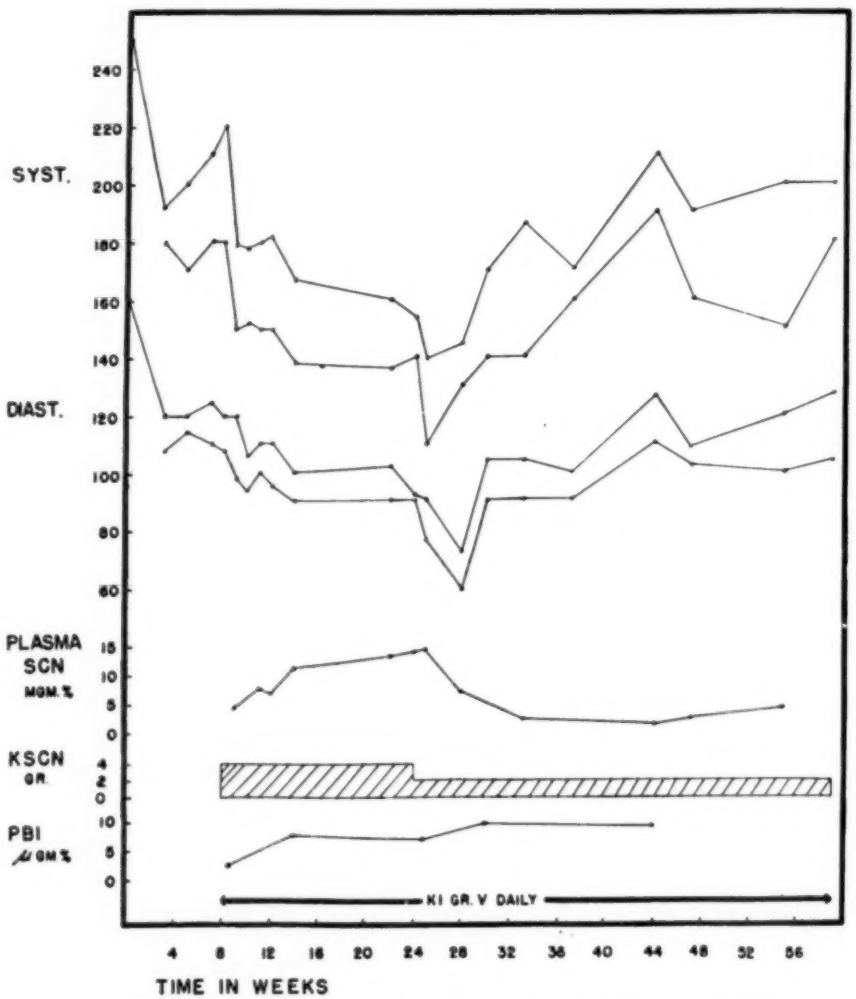

Fig. 1.—Case 1. The effect of KSCN supplemented with KI on blood pressure.

Control observations of PBI and I^{131} uptake were made before any thiocyanate (SCN) therapy was instituted. These determinations were repeated after 5 to 6 weeks of SCN therapy and at varying intervals thereafter. The dose of radioiodine used on these occasions was from 40 to 50 microcuries. The patients were seen at approximately weekly intervals at which times the plasma SCN level was measured, the dosage of the drug altered if necessary, and clinical progress assessed. At each visit, ten to twelve measurements of the blood pressure were taken at intervals of 3 to 4 minutes. This was done at ordinary

room temperature, with the patients lying supine in individual cubicles. All readings were made by the same observer. The double lines on the graphs (Figs. 1 and 2) represent the highest and lowest systolic and diastolic pressures recorded at each visit.

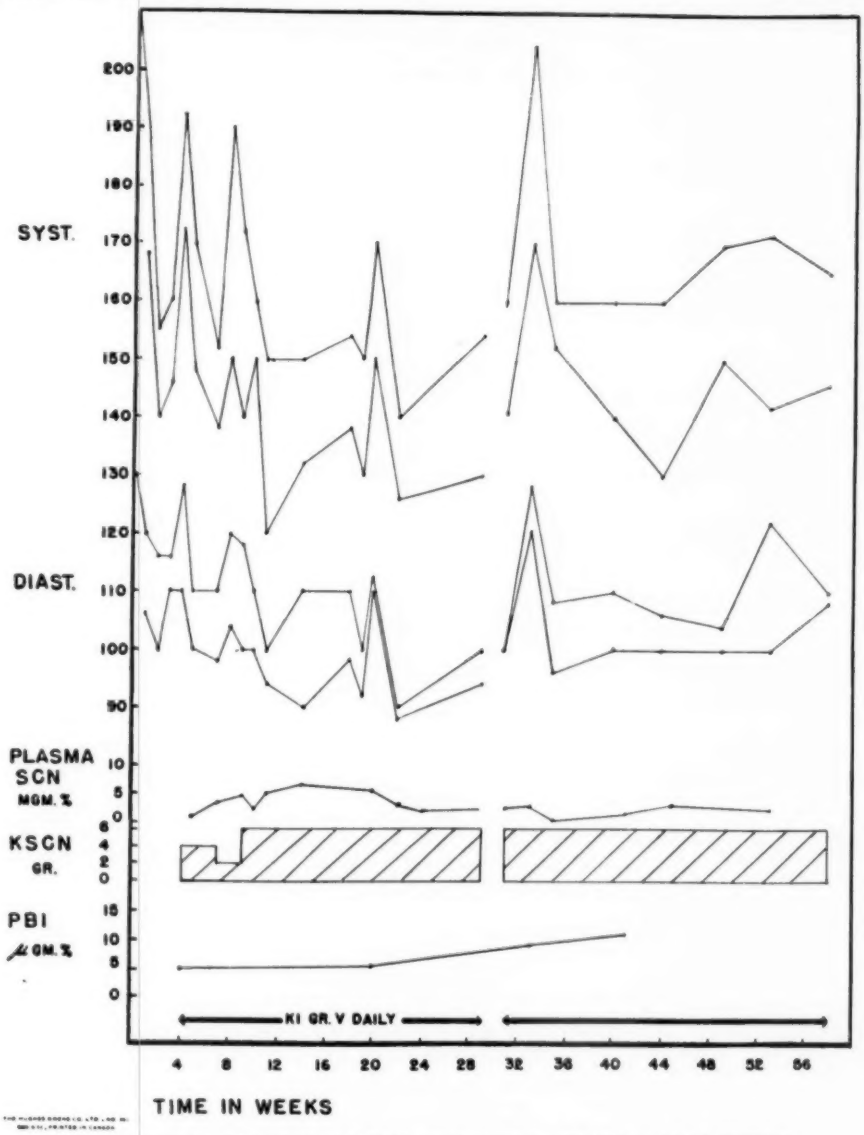

Fig. 2.—Case 2. The effect of KSCN supplemented with KI on blood pressure.

Since simultaneous administration of potassium iodide (KI) will prevent the thyroid depressant action of thiocyanate[16] of the group studied, certain patients had the usual daily doses of SCN supplemented with 330 mg. of KI daily. Their blood pressures and clinical course were followed in the same manner. No tracer studies were done on the latter group, but protein-bound iodine determinations were made.

RESULTS

In Table I are shown the effects of KSCN therapy on the thyroid uptake of iodine and on the plasma PBI before and at various times after starting medication. It will be seen that at 6 to 7 weeks after commencing therapy, when these values were redetermined for the first time, there was a depression of I^{131} uptake which persisted as long as KSCN was continued. Plasma levels as low as 1.3 mg. per cent appeared to be capable of inhibiting the thyroid uptake of iodine to a certain extent.

TABLE I. EFFECT OF THIOCYANATE ON PBI AND THYROID UPTAKE OF I^{131}

Patient 1	Weeks	0	7	16	23	40
PBI μg %		10.6	6.7	3.7	1.0	4.8
RaI 24 hr. uptake % dose		44	9.5	27	28	36
Plasma SCN mg. %		0.1	3.6	3.6	4.0	1.5

Patient 2	Weeks	0	8	13		
PBI μg %		5.7	6.8	5.5	—	—
RaI 24 hr. uptake % dose		22	11.6	20	—	—
Plasma SCN mg. %		0	7.2	0	—	—

Patient 3	Weeks	0	6	14	20	26	33	44
PBI μg %		4.8	6.5	6.0	1.6	2.9	5.3	5.3
RaI 24 hr. uptake % dose		14.5	4.6	3.4	7.4	41.0	7.3	10.0
Plasma SCN mg. %		0.25	1.3	4.8	5.2	1.5	2.0	1.0

Patient 4	Weeks	0	6	16	24	27	58
PBI μg %		—	8.2	3.2	4.6	2.2	3.5
RaI 24 hr. uptake % dose		29.6	8.6	7.1	9.8	9.5	17.0
Plasma SCN mg. %		0.5	4.7	5.2	6.6	3.4	6.5

Patient 5	Weeks	0	6	12	17	26	42
PBI μg %		9.3	5.6	4.3	1.3	—	3.5
RaI 24 hr. uptake % dose		18	13.8	6.0	9.4	20.0	45.0
Plasma SCN mg. %		0.5	4.4	5.1	7.3	2.0	0

The plasma PBI also fell, but usually not as rapidly as the I^{131} uptake and usually not down to the levels associated with clinical hypothyroidism, i.e., less than 2 micrograms per 100 c.c. The fall in PBI was slower and only appeared after an appreciable time of thyroid inhibition, i.e., usually not until 16 weeks. At no time over periods of 40 to 44 weeks on SCN did any subject exhibit any clinical manifestations of hypothyroidism. These patients exhibited the usual blood pressure reductions seen in thiocyanate-treated patients.

That the fall in blood pressure is produced by the SCN itself and not by a hypometabolism resulting from an SCN-induced reduction in thyroid hormone is seen by the results presented for two patients in Figs. 1 and 2. These patients had their daily SCN supplemented with 330 mg. KI daily, sufficient to ensure adequate thyroid uptake of iodine in the presence of SCN.[16] It will be seen that a depression of the blood pressure was also achieved here.

In Case 1, (Fig. 1) on a daily dose of 4 grains KSCN, the plasma level increased from 5 to 14 mg. per cent, the PBI rose from 5 to 7 micrograms per cent, and a demonstrable drop of blood pressure occurred. The mean systolic pressure dropped from 200 to 125, the mean diastolic from 115 to 75 mm. Hg. With a decrease in the dose to 2 grains, KSCN daily, the plasma SCN quickly fell to levels between 2 to 5 mg. per cent, the PBI remained at 7 to 10 micrograms per cent, and the mean pressure returned to 200 systolic, and 118 diastolic.

In Case 2, (Fig. 2) on a daily dose of 6 grains KSCN, the plasma SCN increased to 6.5 mg. per cent, the PBI remained about 5 micrograms per cent, and the mean systolic pressure fell from 190 to 140, the mean diastolic from 115 to 95 mm. Hg. After an interruption of one month on no KSCN, the plasma SCN fell to 2 mg. per cent, the PBI rose to 11 micrograms per cent, the mean pressure rose to 190/125, returning to 155/105 with resumption of 6 grains of KSCN daily.

Similar blood pressure effects occurred in two other patients treated with KSCN and KI. In all these patients the PBI actually rose. This is not indicative of excess thyroid hormone in the circulation but is probably due to the binding of iodide to plasma proteins which occurs when large doses of iodine are administered to euthyroid patients.[17,18]

DISCUSSION

It seems clear that ordinary therapeutic doses of potassium thiocyanate raise the tissue concentrations of SCN to levels capable of interfering with the ability of the thyroid to take up iodine, eventually resulting in a lowered synthesis and output of hormone by the gland. This effect occurs with plasma levels of SCN above 1.3 mg. per cent. None of the subjects studied here ever exhibited signs or symptoms that could be ascribed to hypothyroidism during the course of the investigation. However, in two patients (No. 3 and 5 in Table I) the depression of radioiodine uptake and the lowered PBI reached levels usually encountered in complete athyrosis. It would seem, nevertheless, that some iodine was being utilized by the gland and released to the body as hormone, which would delay the onset of hypothyroidism, a condition that develops slowly after complete cessation of thyroid function.

The satisfactory clinical response in four patients who had KSCN and KI would suggest that the beneficial effects of SCN on hypertension are primarily due to the drug itself and are not mediated through a thyroid depression with consequent lowering of metabolism. The administration of large amounts of iodide with SCN would prevent the inhibiting action of SCN on the thyroid collection of iodide.[9]

SUMMARY AND CONCLUSIONS

1. Data are presented to demonstrate that KSCN administered in therapeutic dosage for the treatment of hypertension interferes with the uptake of iodine and the synthesis of hormone by the thyroid gland.

2. When the thyroid depressant action of thiocyanate is prevented by the simultaneous administration of KI, the usual blood pressure reductions are nevertheless obtained. It is therefore concluded that the hypotensive action of thiocyanate is not dependent on hypometabolism due to depression of thyroid function.

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HEART DISEASE IN INDIA

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THERE is no dearth of statistical studies on the incidence of heart disease, as far as the Western countries are concerned, numerous papers on the subject having been published during the last three decades.[1]

The same, however, cannot be claimed for tropical countries, like India, where the development and study of this aspect of heart disease have been sadly neglected.

Although papers, on the incidence and importance of cardiovascular diseases in India,[2,3,4-14] have appeared within recent years in local journals, they remain inaccessible to Western authors. It is, therefore, with the idea of acquainting the latter, with the problem of heart disease, as it exists in a tropical country like India, that the present paper has been undertaken.

The objects of the present investigation have been to determine (1) the prevalence of heart disease in India, (2) the relative incidence of the various etiologic forms of heart disease, and (3) the characteristics of individual forms of heart disease.

SELECTION AND NATURE OF MATERIAL

During the five-year period, 1941 to 1945 inclusive, 30,104 patients were treated in the medical wards of King Edward Memorial Hospital, Bombay. Of these, 78.5 per cent were males and 21.5 per cent females. Since available accommodation is three times greater for males than females, at this hospital, a correction has been made for this factor, in the presentation of all subsequent sex data.

The majority of patients were drawn from "low income groups," being mostly employed as laborers, mill-hands, and domestic servants.

RESULTS OF INVESTIGATION

Incidence of Heart Cases.—Of the 30,104 medical cases studied, 1,860 cases were of organic heart disease, giving a percentage incidence of 6.2 per cent (or about one case in seventeen). Of these, 1,361 were males and 499 females.

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Age incidence: Patients ranged in age from 4 years to 100 years, with an average of 43.2 years. The percentage incidence, per age decade of life, was as follows, viz., 1 per cent of cases in the first decade, 10.1 per cent in the second, 15.2 per cent in the third, 19.7 per cent in the fourth, 24.3 per cent in the fifth, 18.5 per cent in the sixth, 8.6 per cent in the seventh, 2.6 per cent in the eighth, and 0.05 per cent of cases over the age of 80 years.[5] Therefore, of these cases, 78 per cent were between the age limits of 20 and 59 years, 11 per cent below the age of 19 years, and 11.2 per cent over the age of 60 years. The highest incidence of cases was observed in the fifth decade of life.

Racial incidence: A relatively higher incidence of organic heart disease was noted among the Christians, Parsees, and Jews, than among the Hindus. Hindus, Moslems, and Christians accounted for 70.2 per cent, 14.9 per cent and 12.2 per cent, respectively, of all medical admissions, and for 62.3 per cent, 17.2 per cent and 14.8 per cent, respectively, of cases of organic heart disease.

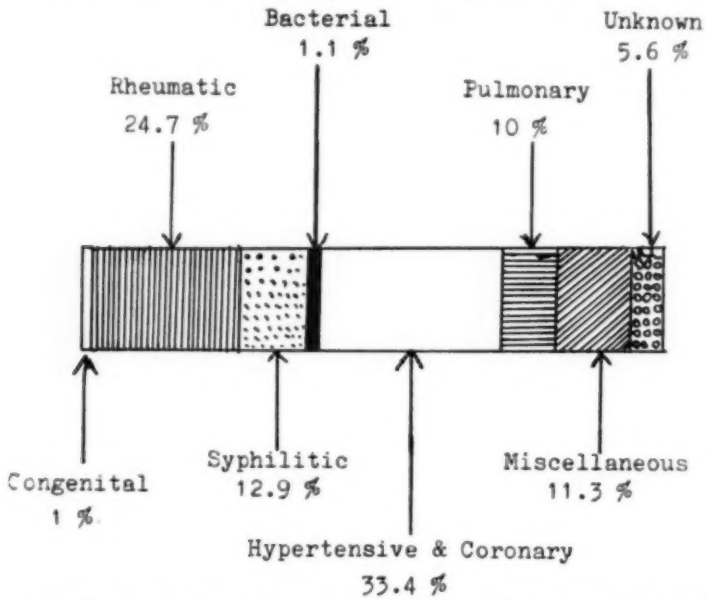

Fig. 1.—Percentage incidence of the various etiologic forms of organic heart disease.

Etiologic incidence: The percentage distribution of cases of organic heart disease into etiologic groups worked out as follows, viz., (1) congenital, 1 per cent; (2) rheumatic, 24.7 per cent; (3) syphilitic, 12.9 per cent; (4) bacterial, 1.1 per cent; (5) hypertensive, 29 per cent; (6) coronary, 13.5 per cent; (7) pulmonary, 10 per cent; (8) miscellaneous, 11.3 per cent; and (9) of unknown origin, 5.6 per cent (Fig. 1). Group (8) included cases of diverse etiology such as thyrotoxicosis, anemia, vitamin-deficiency, and traumatic heart disease. In groups 5 and 6 each, 171 cases, with both hypertensive and coronary involvement, had to be included.

From the point of view of incidence, the two most important groups were the hypertensive and rheumatic, being jointly responsible for 53.7 per cent of all cases.

Etiologic Factors According to Age Groups.—It is obvious from Table I, that the relative importance of any etiologic factor, varies greatly with the age group studied. For instance, rheumatism accounts for about 60 per cent of the cases under the age of 30 years, but for only 3 per cent over the age of 50. Coronary disease and hypertension are jointly responsible for only 18 per cent of the cases under the age of 40, and for 50 per cent over the age of 50 years.

TABLE I. PERCENTAGE DISTRIBUTION OF THE VARIOUS ETIOLOGIC FORMS OF ORGANIC HEART DISEASE PER AGE DECADE OF LIFE*

AGE GROUP (YR.)	CONGENITAL	RHEUMATIC	SYPHILITIC	BACTERIAL	HYPERTENSIVE CORONARY	PULMONARY	MISC. AND UNKNOWN
0– 9	21.1	42.4	0	0	21.1	0	15.6
10– 19	3.3	71.1	1.3	2.7	11.4	1.3	9.1
20– 29	1.4	53.9	7.0	1.8	16.8	2.1	17.0
30– 39	1.4	27.0	21.6	2.2	21.9	3.8	22.1
40– 49	0.2	6.9	16.4	0.7	41.4	14.7	19.7
50 –59	0	4.9	13.1	0	46.5	15.9	19.6
60– 69	0	0	11.9	0	58.1	20.6	9.4
70– 79	0	0	4.0	0	58.4	23.0	14.6
80–100	0	0	0	0	0	0	100.0
All ages	1.0	24.7	12.9	1.1	33.4	10.0	16.9

*Figures expressed in percentages.

Racial incidence: Four racial groups were recognized, viz., Hindus, Moslems, Christians, and "Others" (mainly, Parsees and Jews). The racial incidence, in percentages, for individual etiologic groups has been worked out in Table II.

It will be apparent from Table II, that the racial incidence is not uniform in the individual etiologic groups. For instance, while the syphilitic group shows a high incidence of Moslems, the hypertension and coronary groups exhibit a relative preponderance of Christians and "others".

TABLE II. PERCENTAGE DISTRIBUTION OF RACIAL GROUPS IN THE VARIOUS ETIOLOGIC TYPES OF HEART DISEASE*

GROUP STUDIED	NO. CASES	MOSLEM	HINDU	CHRISTIAN	OTHERS
Congenital	19	89.4	10.6	0	0
Rheumatic	461	71.1	17.2	8.7	3.0
Syphilitic	240	56.3	27.9	12.9	2.9
Hypertensive coronary	788	50.6	15.2	23.4	10.8
Pulmonary	186	75.3	12.4	9.1	3.2
Bacterial	20	75.0	15.0	5.0	5.0
Miscellaneous and unknown	315	66.4	16.8	12.6	4.2
All heart cases	1,860	62.3	17.2	14.8	5.7
All medical cases	30,104	70.2	14.9	12.2	2.7

*Figures expressed in percentages.

Multiplicity of factors: Maher and associates[15] were able to demonstrate multiple etiologic factors in 30 per cent of a series of 5,000 cases in Chicago.

In the present series, associated etiologic factors were demonstrable in 7.3 per cent of cases of the rheumatic, 15 per cent of the syphilitic, 52 per cent of the hypertensive, 69.8 per cent of the coronary, and 10.8 per cent of the pulmonary groups. The high incidence in the coronary and hypertensive groups was noteworthy.

Investigation of Individual Etiologic groups.—The congenital and bacterial groups were considered too small for the purposes of investigation. The miscellaneous group and the group of "unknown" causes, being comprised of heterogeneous and obscure factors, were considered unsuitable for further study. Further investigation was therefore confined to the remaining etiologic groups.

THE RHEUMATIC GROUP

The high incidence and importance of rheumatic heart disease are well recognized in Western countries. According to Paul,[16] there are about 840,000 people with rheumatic heart disease per 100,000,000 population. The incidence of rheumatic heart disease has been variously reported, in different statistical analyses as 3.4 per cent to 62 per cent.[5-7]

Regarding the incidence of rheumatic heart disease in the tropics, there have been major differences of opinion. On the one hand, Rogers,[17,18] Clarke,[19,20] and Cowan and Ritchie[21] have regarded the disease as rare or even nonexistent in the tropics; on the other, Hughes and Yusuff,[22] Stott,[23-25] Banerjea,[26] Kelly,[27] Kutumbiah,[28] Gunewardene,[2] Raghvan,[29] Fernando,[3] and Vakil[4-7] have reported its high incidence in various parts of Bengal, United Provinces, Punjab, Madras, Ceylon, and Bombay.

Incidence.—In my series of cases, 461 cases or 24.7 per cent displayed evidences of rheumatic heart disease. Besides these, there were forty-nine cases of rheumatic fever or febrile rheumatic arthritis and five cases of chorea, free of cardiac involvement. The ratio of rheumatic cases with cardiac involvement to those without worked out at 8.5 to 1.

The incidence of chorea was very small, accounting for 3 per cent of the rheumatic heart cases and for 1 per cent of all heart cases.

Sex incidence: In the present series, the male to female ratio worked out at 1 to 1.9. It has been reported as 1 to 1.2 by White and Jones,[30] and 1 to 1.1 by Fernando.[3]

Age incidence: The 461 cases of rheumatic heart disease showed the following percentage incidence per age decade, viz., 1.7 per cent of cases in the first decade of life, 31.3 per cent in the second, 33.1 per cent in the third, 23.7 per cent in the fourth, 6.7 per cent in the fifth, and 3.7 per cent in the sixth; no cases were observed after the age of 60 years.

The highest incidence was therefore observed in the third, second, and fourth decades of life, in that order, and they were jointly responsible for 88 per

cent of cases. The low incidence of 1.7 per cent for the first decade and 3.7 per cent for cases over 50 years is noteworthy.

The peak of incidence was in the second decade for males and in the third for females.

Racial incidence: According to Poynton and Schlesinger,[32] white-skinned races are more susceptible to the disease than the dark races. This was not evident in my series, the incidence being about the same in the different racial groups.[5-7]

Seasonal incidence: Although medical opinion accepts the importance of "damp" and "chill" in the incidence of rheumatic infections,[32,33] in my series, the incidence, paradoxically enough, was higher during the "hotter" months of the year. This may be due partly to the strong sea breeze and partly to the tendency to excessive sweating in the hot summer months of Bombay.

Incidence of valvular lesions: Of the 461 cases, valvular lesions were demonstrable in 90 per cent. Mitral stenosis (isolated or associated with other valvular lesions) was noted in 69 per cent of cases, mitral incompetence in 64.3 per cent, aortic incompetence in 19.5 per cent, and aortic stenosis in 5.7 per cent. Of all rheumatic heart cases, 45 per cent exhibited mitral stenosis with insufficiency, 13 per cent isolated mitral stenosis, and 10 per cent isolated mitral incompetence.

Aortic stenosis with incompetence was observed in 1.3 per cent of cases, aortic stenosis alone in 1.1 per cent, and aortic incompetence alone in 3.1 per cent. Combined mitral and aortic lesions were observed in 19.3 per cent.

Of the males 71 per cent displayed mitral valve disease, 7.3 per cent aortic disease, and 21.7 per cent combined mitral and aortic disease. The corresponding percentages for females were 85.8 per cent, 3.6 per cent and 10.6 per cent, respectively. The lower incidence of aortic lesions in females was noteworthy.

The Mitral Group.—Of the 314 cases with isolated involvement of the mitral valve, 66.2 per cent exhibited both stenosis and incompetence.

Of these cases of mitral disease 2.4 per cent were in the first decade of life, 31.8 per cent in the second, 32.2 per cent in the third, 23.9 per cent in the fourth, 6.5 per cent in the fifth, and 3.2 per cent in the sixth decade. The highest incidence was noted in the third decade of life; 88 per cent of the cases were between the ages of 10 and 39 years and only 10 per cent over 40 years of age.

A relative preponderance of males was noted in the second and fifth decades.

The "highest" incidence of cases was noted in the third decade of life for mitral stenosis and in the second for mitral incompetence. A relatively higher male incidence was observed in the mitral stenosis group.

Hypertension in mitral stenosis: The frequent association of hypertension with mitral stenosis has been commented upon in the literature.

Of the 268 cases of mitral stenosis, diastolic hypertension was observed in only 6.4 per cent. In the remaining cases, the average blood pressure readings were actually lower than normal.

In the *aortic group*, of rheumatic cases 56 per cent showed incompetence and 44 per cent stenosis with incompetence. The highest incidence was noted in the fourth decade of life, or a decade later than in the case of the mitral group.

While 34 per cent of the cases in the mitral group were over the age of 30 years, the corresponding figure for the aortic group was 52 per cent.

The relative incidence of males was two-and-one-half times greater in the aortic than in the mitral group.

Cardiac failure: Cardiac failure was noted in 81.4 per cent of the cases of rheumatic heart disease. Of these, 48.6 per cent displayed right-sided failure, 14.9 per cent left-sided, and 36.5 per cent right-and-left-sided failure.

Auricular fibrillation was observed in 8.2 per cent of the cases of rheumatic heart disease. The age range was 10 to 56 years with an average of 33.6 years; the highest incidence (37 per cent) was observed in the fourth decade of life.

SYPHILITIC HEART DISEASE

After rheumatism, syphilis is "the second most common and important cause of infectious cardiovascular disease." The incidence of syphilitic heart disease has been variously reported, in the literature, as 1.1 per cent to 31.6 per cent of all cardiac cases, being particularly high in Negroes.[1,5]

Incidence: Cardiovascular syphilis accounted for 12.9 per cent of cardiac and 0.79 per cent of medical admissions in my series. The incidence was relatively high among Moslems, the percentage incidence of Hindus, Moslems and Christians being 56.5 per cent, 27.5 per cent and 13.4 per cent, respectively, for the syphilitic group, and 62.3 per cent, 17.2 per cent and 14.8 per cent, respectively, for the entire cardiac group.

Patients ranged in age from 16 to 78 years with an average of 43.5 years. Of the cases 63.3 per cent were between the ages of 30 and 49 years, 9.1 per cent under the age of 30, and 8.7 per cent over 60 years of age.

In all reported statistics on syphilis, there has been a great preponderance of males.[1] In my series, the male-to-female ratio was 7.7 to 1.

Clinical Groupings.—The 240 cases were classified as follows, viz., (1) Syphilitic aortic regurgitation, 55.9 per cent; (2) aortic aneurysms, 26.7 per cent; (3) coronary involvement, 1.3 per cent; (4) other forms, including myocarditis and pulmonary endarteritis, 16.1 per cent. Of the cases, 82.7 per cent displayed either aortic regurgitation or aneurysm formation or both, 15.5 per cent primary myocardial involvement and 1.3 per cent, coronary involvement. The high incidence of primary myocardial involvement was noteworthy.

Syphilitic aneurysms: There were 64 cases of aneurysm, accounting for 26.7 per cent of cases of cardiovascular syphilis, 3.5 per cent of cases of organic heart disease and 0.21 per cent of medical admissions. Sixty-four per cent of the aneurysm cases were between 30 and 49 years of age, only 4.7 per cent being over the age of 60. As many as 6 cases (9.4 per cent) were under the age of 30 years. This is surprising, in view of the reported rarity of aneurysm under that age.[36] The male-to-female ratio for syphilitic aneurysms was 10 to 1.

The distribution of aneurysm cases, according to *site*, was as follows, viz., (1) ascending aorta and aortic arch, 46 cases (71.9 per cent); (2) descending

thoracic aorta, 8 cases (12.5 per cent); (3) abdominal aorta, 7 cases (10.9 per cent); (4) other sites, (viz., innominate, femoral and popliteal arteries), 3 cases (4.7 per cent). Thoracic aneurysms were 7.7 times as frequent as abdominal aneurysms.

HYPERTENSIVE HEART DISEASE

In India, the incidence of hypertensive heart disease in cardiac patients has been reported as 13 per cent for hospital and 25 per cent for private cases by Gunewardene,[2] 18.3 per cent by Sen Gupta,[37] 16 per cent by Kutumbiah,[28] and 11.9 per cent by Raghvan,[29] on the basis of autopsy studies.

In my series, hypertensive heart disease, accounted for 29 per cent of the heart cases and 1.8 per cent of the medical cases. Of the hypertensive heart cases 92.9 per cent were of essential, primary, or nonrenal type.

The *age distribution* of these cases was as follows: 0.6 per cent of cases in the first decade of life, 4 per cent in the second, 8.1 per cent in the third, 12.1 per cent in the fourth, 27.7 per cent in the fifth, 27.7 per cent in the sixth, 16.4 per cent in the seventh, 4.9 per cent in the eighth, and no cases after the age of 80 years. The fifth and sixth decades of life were jointly responsible for 55 per cent of the cases; only 12.7 per cent of the cases were below the age of 30, and 21 per cent over the age of 60 years.

The male-to-female ratio was 1 to 1.1 for the series. In the renal or nephritic group, 84 per cent of the cases were between the age limits of 10 and 29 years, only 13 per cent being over 30.

The essential, primary, or benign group of 500 cases was, by contrast, characterized by a high incidence of older age groups. The highest incidence was observed in the fifth and sixth decades of life; only 6.4 per cent of the cases were below 30 years of age, there being two cases under ten, (boys aged 9 years and 4½ years, respectively). Genuine cases of essential hypertension, in childhood, have been reported in the past by Hutchison and Moncrieff,[38] Holzmann,[39] Taussig and Remsen,[40] and Fishberg.[41]

Associated coronary disease: A high incidence of coronary involvement in hypertensive cases has been noted.[41] In my series, the incidence was 34.2 per cent for all age groups and 42.3 per cent for cases over 70. It was 41.9 per cent for males and only 12.8 per cent for females.

Cardiac failure: The incidence of cardiac failure was 65.6 per cent; of isolated left-sided failure, 10.8 per cent; right-sided failure, 1.6 per cent; and "mixed" failure, 53.2 per cent.

Other complications: Cerebral hemorrhage was noted in 6.4 per cent of cases; cerebral thrombosis in 10.4 per cent; hypertensive encephalopathy in 7 per cent; uremia, in 3.2 per cent; auricular fibrillation in 2.8 per cent; heart block in 4.6 per cent; paroxysmal tachycardia in 0.4 per cent; Meniére's syndrome in 1.2 per cent; functional aortic insufficiency in 1.8 per cent; subarachnoid hemorrhage in 0.2 per cent; and mesenteric thrombosis in 0.2 per cent.

Of the cases 34.2 per cent exhibited associated coronary disease, 4.8 per cent diabetes, 7.2 per cent syphillis, 5.6 per cent emphysema, and 3.8 per cent rheumatic heart disease.

CORONARY HEART DISEASE

The incidence of coronary disease, as reported in clinical studies from different parts of the world, shows wide variations.[1]

In the present series, coronary disease accounted for 13.5 per cent of cardiac and 0.83 per cent of medical cases. Of the coronary cases, 68.4 per cent were associated with hypertension.

The age incidence of coronary heart cases was as follows, viz., 4 per cent of cases under the age of 30 years, 12.4 per cent in the fourth decade of life, 35.6 per cent in the fifth, 26.4 per cent in the sixth, 16.4 per cent in the seventh, and 5.2 per cent in the eighth.

The highest incidence (35.6 per cent) was observed in the fifth decade, or a decade earlier than reported in western statistics. Of the cases, 48 per cent were under the age of 40; and three cases actually below 20 years of age.

In published papers[42,43] on the subject of coronary disease, there has been a striking preponderance of males. In my series, the male-to-female ratio was 2.9 to 1 for all cases, 1.3 to 1 for cases below 30 years of age, and 1 to 1.9 for cases over 70.

Recent studies[44-46] have emphasized the importance of the "racial factor" in the incidence of coronary disease. In the present series, the incidence of coronary disease was definitely higher among Christians, Parsees and Jews than among Hindus and Moslems. While the percentage incidence of the four racial groups, viz., Hindus, Moslems, Christians, and "others", was 62.3 per cent, 17.2 per cent, 14.8 per cent and 5.7 per cent, respectively, for cases of organic heart disease, it was 55.6 per cent, 17.8 per cent, 18.4 per cent and 8 per cent, respectively, for the coronary group.

Coronary Thrombosis.—The age incidence, of cases of acute coronary occlusion, was as follows, viz., 5.1 per cent of cases under the age of 30 years, 11.3 per cent in the fourth decade of life, 40 per cent in the fifth, 24.4 per cent in the sixth, 14.8 per cent in the seventh, and 4.4 per cent in the eighth.

Of my cases, 64.4 per cent were between the age limits of 40 and 59 years, 56.4 per cent under the age of 50, and 19.2 per cent over the age of 60. Whereas 56.4 per cent of cases were under 50 years of age, only 21.6 per cent of White's cases[1] were under that age. In other words, younger age groups figured far more prominently in my series.

Juvenile or youthful cases of coronary thrombosis have been reported from time to time.[1] In my series, 16.4 per cent of the cases were below the age of 40 years, there being as many as six cases under the age of 30 years. The youngest case was that of a girl, aged 7½ years, with a typical pattern of posterior wall myocardial infarction. In all reported studies, there has been a striking preponderance of males. In my series, the male-to-female ratio worked out at 3.2 to 1.

Cardiac failure was reported in 66 per cent of the cases of coronary thrombosis by Master and associates.[47] In my series, it was noted in 68.3 per cent of the cases. Cardiac arrhythmias were noted in 34.8 per cent of cases, diabetes mellitus in 3.5 per cent, and syphilis in 7 per cent.

Angina Pectoris.—The incidence of angina pectoris in cardiac cases has been reported by White and Jones[30] as 11.8 per cent. In my series, the incidence was 5.7 per cent.

The age incidence of cases of angina pectoris was as follows, viz. 3.8 per cent of cases were under the age of 30 years, 11.3 per cent in the fourth decade of life, 31.1 per cent in the fifth, 28.3 per cent in the sixth, 18 per cent in the seventh, and 7.5 per cent in the eighth. The "peak" of incidence was noted in the fifth decade (31.1 per cent). The male-to-female ratio has been reported as 3 to 1 by White[1] and 5.2 to 1 by Bramwell and King.[31] In my series, it was 2.7 to 1.

CHRONIC COR PULMONALE

According to the majority of Western statistics, pulmonary heart disease accounts for but a small percentage (0.5 to 3.7 per cent) of cases of organic heart disease. In my series, the incidence of pulmonary heart disease was remarkably high, being 10 per cent of cardiac and 0.62 per cent of all medical cases.

Age incidence: The majority of the cases were middle-aged, 64.4 per cent of the cases being between the age limits of 40 and 59 years, 11.9 per cent under the age of 40 and 23.7 per cent over the age of 60. The average age for the series was 51.5 years.

The male-to-female ratio was 1.7 to 1. Asthma, emphysema, and chronic bronchitis were either singly or jointly responsible for 79.4 per cent of the cases. The remaining cases were accounted for by diverse conditions, like pulmonary tuberculosis, bronchiectasis, massive adhesions, pneumonosis, and pulmonary endarteritis. Cardiac failure was noted in 64 per cent of the cases.

SUMMARY

1. A statistical study is presented of 1,860 cases of organic heart disease, from a medical population of 30,104 patients, observed in Bombay, India. The incidence of organic heart disease works out at 6.2 per cent.

2. The incidence of heart disease is investigated from the points of view of age, sex, and race. The highest incidence of cases (24.3 per cent) is observed in the fifth decade of life; 62.8 per cent of the cases are between the age limits of 30 and 59 years. A relatively higher incidence is observed among the Christians, Parsees, and Jews than among the Hindus and Moslems.

3. Cases of organic heart disease are classified into nine etiologic groups, viz., (1) congenital, 1 per cent; (2) rheumatic, 24.7 per cent; (3) syphilitic, 12.9 per cent; (4) bacterial, 1.1 per cent; (5) hypertensive, 29 per cent; (6) coronary, 13.5 per cent; (7) pulmonary, 10 per cent; (8) miscellaneous, 11.3 per cent; and (9) "of unknown origin", 5.6 per cent.

4. The rheumatic, syphilitic, hypertensive, coronary, and pulmonary groups of heart disease are individually investigated, from the points of view of incidence, age, sex, race, associated etiologic factors and complications.

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A CLINICAL STUDY OF THE EFFECTS OF INTRAVENOUS RESERPINE (SERPASIL)* IN HYPERTENSIVE PATIENTS

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THE past several years have seen the introduction of many new drugs capable of reducing blood pressure in patients with hypertension. Clinical reports indicate that hypertensive patients receiving extracts of Rauwolfia serpentina exhibit a moderate reduction in blood pressure and symptomatic improvement.[1,2] Although a definite sedative effect has been recognized, the exact reason for the fall in blood pressure in man has not been determined.

It is the purpose of this report to present observations on a crystallized pure alkaloid from Rauwolfia serpentina, reserpine (Serpasil), given as a single intravenous injection to patients with hypertension, to determine the degree of its hypotensive properties and to compare its hypotensive effects to those of sedation with sodium Amytal.

METHODS AND MATERIALS

A group of twenty-three patients with moderate to severe hypertension from the wards of the University of Wisconsin Hospitals were the subjects for this study. There were twelve men and eleven women whose ages ranged from 40 to 64 years with an average age of 50 years. Each patient was subjected to the usual clinical and laboratory examinations for evaluating hypertension, including routine urinalysis, phenolsulfonphthalein excretion, urinary concentration, blood nonprotein nitrogen determination, electrocardiogram, chest roentgenogram, and eye ground examination. The majority of the patients had intravenous pyelography and Regitine tests. Fifteen of the twenty-three patients had sodium Amytal tests.

Control values were obtained by multiple daily blood pressure determinations made by nurses, senior medical students, house and attending staff members. Patients were ambulatory while in the hospital and observed from 4 to

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TABLE I. BLOOD PRESSURE RESPONSE OF PATIENTS RECEIVING RESERPINE (SERPASIL) AND SODIUM AMYTAL TEST

PATIENT	SEX	AGE	CONTROL B.P.		B.P. AFTER RESERPINE		MABP FALL	DOSE MG.	SIDE EFFECTS	B.P. AFTER SODIUM AMYTAL		MABP FALL
			AV.	MEAN	AV.	MEAN				AV.	MEAN	
1	M	49	196/125	149	177/114	135	14	1.0	NS & FF	165/109	128	21
2	F	43	232/146	175	206/133	157	18	1.0				
3	M	58	201/129	153	140/87	105	48	1.0	FF			
4	M	43	173/114	134	135/94	108	26	0.75		136/97	110	24
5	F	57	215/120	152	201/118	146	6	1.0	NS & FF			
6	F	53	205/117	146	189/106	134	13	0.5	FF			
7	F	48	204/118	147	170/107	128	19	1.0	NS & FF	152/101	118	29
8	M	58	212/118	143	193/105	134	9	1.0		202/113	143	0
					186/102*	130	13	1.0	NS & S			
9	F	48	213/119	150	169/103	125	25	1.0	NS	148/95	113	37
10	M	54	167/99	122	136/89	105	17	0.75	NS	122/81	95	27
11	M	52	190/120	143	162/101	121	22	1.0	NS	184/122	143	0
12	M	45	195/119	144	163/99	117	27	1.0	Ex.	165/92	116	28
13	F	53	198/125	149	144/100	115	34	1.0	NS,FF,NM	116/81	97	52
14	F	45	207/112	144	197/104	135	9	0.5		169/118	125	19
15	F	49	164/100	121	144/88	107	14	0.5	NM			
16	F	42	195/111	139	165/92	116	23	1.0	NS	130/77	95	44
17	M	50	193/111	138	169/93	118	20	1.0				
18	F	48	198/120	146	152/95	114	32	1.0	FF & S			
19	M	58	222/122	155	206/117	147	8	1.0	NS	189/113	138	17
					214/119*	151	4	2.0				
20	F	64	197/120	148	171/99	123	25	1.0	NS			
21	M	50	236/135	169	210/122	151	18	1.0	NS	179/120	140	29
					202/115*	144	25	2.0	NS & FF			
22	M	47	162/104	123	137/90	108	15	1.0	NS	143/98	106	17
23	M	40	177/112	134	177/110	132	2	1.0	NS	140/102	115	19
Mean		50	198/118	145	170/103	125	20			156/101	119	26

MABP—Mean arterial blood pressure
BP —Blood pressure (mm. Hg)
M —Male
F —Female
Av. —Average
FF —Facial flush
S —Sleepy
NM—Nightmare
Ex —Excitement
* —Second dose after 24 hours
NS—Nasal stuffiness

10 days prior to the drug study. Because of the difficulty in establishing a control level in a group of hypertensive patients, the control blood pressure was calculated by averaging the five highest and five lowest pressures recorded during the entire period of hospitalization exclusive of the experimental period. The mean arterial blood pressure (MABP) was calculated by adding one-third of the pulse pressure to the diastolic pressure.

The sodium Amytal test was performed on fifteen of the twenty-three patients. Blood pressures were taken hourly from 6:00 P.M. to 7:00 A.M. Three equally divided doses of sodium Amytal, 200 mg. each, were administered orally at 9:00 P.M., 10:00 P.M. and 11:00 P.M. Each patient was found to be sleeping one hour after having taken the first 200 mg. dose. Amytal effect was estimated by averaging the pressures recorded from 10:00 P.M. to 7:00 A.M.

Each patient received a single intravenous injection of reserpine and remained ambulatory. The dose varied from 0.5 to 1.0 mg. The drug was given early in the afternoon and blood pressure determinations were taken (in the supine position) at one-half hour intervals for the first 4 to 6 hours and then hourly until 9:00 P.M. Pressures were taken at least four times on the following day and one pressure was recorded on the third day. Further follow-up was not possible because many of the patients were discharged from the hospital at this time. A minimum of fifteen determinations were obtained on each patient during the two days following intravenous reserpine. The mean average of these determinations represents the blood pressure following drug administration.

RESULTS

The following represent average control values for the group of twenty-three patients. Systolic pressures varied from 162 to 235 mm. Hg, diastolic pressures from 99 to 146 mm. Hg, and the calculated MABP from 121 to 175 mm. Hg. The mean was 198/118 with calculated MABP of 145 mm. Hg (Table I).

Twenty-two of the twenty-three patients had a slight to moderate fall in systolic, diastolic, and MABP. The average pressure of the group fell from the control of 198/118 mm. Hg to 170/103 mm. Hg. The calculated MABP was reduced from 145 mm. Hg to 125 mm. Hg.

Following sodium Amytal the mean average was found to be 156/101 mm. Hg (MABP = 119 mm. Hg). This represented a reduction of 26 mm. Hg when compared with the average control value obtained during the period of hospital observation.

The group was divided into three classifications according to changes in MABP following administration of the drug. Class I includes those patients having a fall of 20 mm. Hg or more and/or a reduction to normotensive levels (140/90 or below). Thirteen of the twenty-three patients fell into this category (Table IIA). Class II includes those patients whose pressures fell from 10 to 20 mm. Hg and Class III, those patients whose pressures fell less than 10 mm. Hg. There were five patients in each of the latter two classifications.

The average age for the patients in Class I was the same as that for the entire group, 50 years. These patients' control average pressure was 139 mm. Hg.

* —Second dose after 24 hours
NS—Nasal stuffiness
AV. —Average

The average pressures for the 48 hours following the single injection of the drug was 114 mm. Hg, an average MABP fall of 25 mm. Hg. Eight of the thirteen patients had sodium Amytal tests. The average pressure fell to 109 mm. Hg, and the average MABP fall was 30 mm. Hg (Table IIB).

TABLE IIA. CLASSIFICATION OF PATIENTS ACCORDING TO RESPONSE TO RESERPINE (SERPASIL)

CLASS	AV. AGE	NUMBER OF PATIENTS	DEGREE OF MABP RESPONSE	CONTROL AV. MABP	AFTER RESERPINE		NO. SHOWING SIDE EFFECTS
					AV. MABP	MABP FALL	
I	50	13	>20 mm. Hg or Normotensive	139	114	25	11
II	49	5	10–20 mm. Hg	157	141	16	5
III	52	5	<10 mm. Hg	146	139	7	3

The average age for the patients in Class II was 49 years. The average MABP fell from 157 mm. Hg to 141 mm. Hg, a fall of 16 mm. Hg. Three of the five patients had sodium Amytal tests with a fall of 28 mm. Hg.

The average age for patients in Class III was 52 years. The average MABP was 146 mm. Hg which fell to 139 mm. Hg, a fall of 7 mm. Hg. Four of the five patients had the sodium Amytal test with a fall of 16 mm. Hg.

One patient (Case 8) who showed only a minimal response to 1.0 mg. of reserpine was given an additional 1.0 mg. after 24 hours, and two other patients, one (Case 19) who showed a minimal response and one (Case 21) who showed a moderate response, were given an additional 2.0 mg. of the drug after 24 hours. There was no appreciable additive effect noted with the second administration, and the results of the first drug injection were used in all calculations.

TABLE IIB. RESPONSE OF PATIENTS TO SODIUM AMYTAL TEST

CLASS	AV. AGE	NUMBER OF PATIENTS	AFTER SODIUM AMYTAL	
			AV. MABP	MABP FALL
I	50	8	109	30
II	49	3	129	28
III	52	4	130	16

Nineteen of the twenty-three patients experienced mild side effects, the majority having nasal stuffiness and facial flush. Several patients complained of being sleepy and lethargic. One patient (Case 12) became tense, anxious, and excited. Two patients reported that they had nightmares. All the patients

showed a decrease in heart rate. These clinical reactions, except for the facial flush, have been reported previously in patients given either the crude root[1,2] or reserpine[3] orally.

The lowest blood pressure determination was observed 1½ to 4 hours following drug injection.

DISCUSSION

In this series of twenty-three patients the response to intravenous reserpine could not be predicted by the degree of hypertension. Thus some patients who were moderately hypertensive and considered clinically in the "neurogenic phase" (Cases 6, 14, and 23) failed to have a significant fall in their mean pressures. Contrariwise, patients who appeared to have "sustained" hypertension (Cases 3, 13, and 20) as well as the added factors of age and concomitant arteriosclerosis, showed a moderate decrease in blood pressure. Whether or not the patient's immediate response to a single intravenous dose can be used as a screening test for successful therapy with the alkaloids of Rauwolfia was not the purpose of this study. Some information will be obtained by further observation of this group while on chronic oral therapy. At the present time, and unlike the titration of the more potent hypotensive agents such as hexamethonium or the veratrum derivatives, the only practical means of determining individual response to Rauwolfia is prolonged administration.[3,4]

This study raises the question as to whether there is more than a coincidental relationship between patients showing a response to reserpine and those responding to sodium Amytal (Tables II A and II B). Patients in Class I had an average mean fall of 25 mm. Hg after reserpine and 30 mm. Hg with sodium Amytal. Class II patients fell 16 mm. Hg after reserpine and 28 mm. Hg with sodium Amytal. The average mean fall in Class III was 7 mm. Hg after reserpine and 16 mm. Hg with sodium Amytal. Three of the five patients in Class II (Cases 2, 7, and 21) had a decrease in their calculated MABP of 18 to 19 mm. Hg following the injection of reserpine. They were, therefore, included in Class II, although their blood pressure fall approximated the reduction seen in Class I patients.

Thus of the eleven patients in Classes I and II who had the Amytal test, only two (Cases 11 and 22) failed to have a fall in the mean pressure of 20 mm. Hg or more. After Amytal, Case 22 showed a mean fall of only 17 mm. Hg, but the final average pressure was in the normotensive range. Of the four patients in Class III who had the Amytal test, none showed a response greater than 20 mm. Hg though one patient's pressure (Case 23) fell to normotensive levels. Generally, patients who showed excellent decreases in pressure with sodium Amytal responded well to the crystallized alkaloid.

From these correlations, it is of interest to speculate that patients who show significant blood pressure reduction with sodium Amytal might also respond to the alkaloids of Rauwolfia serpentina. Also, since the degree of reduction in most instances is comparable, the ability of the Rauwolfia compounds to reduce blood pressure may be primarily related to the drug's known sedative effect rather than to a specific action upon the cardiovascular system. Sodium Amytal

decreases the mean arterial blood pressure by decreasing cardiac output while the total peripheral resistance remains fairly constant.[5] It remains to be seen if Rauwolfia serpentina accomplishes blood pressure reduction in a similar manner.

CONCLUSIONS

1. The effect of a single intravenous injection of reserpine (Serpasil) was studied in twenty-three hospital patients with moderate to severe hypertension.
2. In thirteen of these patients there was a fall in blood pressure to normotensive levels and/or a reduction in calculated MABP of 20 mm. Hg or more.
3. Nineteen of the twenty-three patients experienced mild side effects characterized by nasal stuffiness, facial flush, and lethargy.
4. A sodium Amytal test was performed in fifteen of the twenty-three patients and the blood pressure response was compared with the effect of intravenous reserpine. Generally, patients in whom the MABP fell 20 mm. Hg or more with sodium Amytal showed a comparable blood pressure reduction following intravenous reserpine.

ADDENDUM

Since this manuscript was submitted for publication, we have given an additional sixteen patients 4.0 mg. of reserpine as an intravenous infusion over a one-half to one-hour period. The magnitude of blood pressure decrease was similar to the response presented here except that every patient had a fall in MABP of greater than 10 mm. Hg.

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PATTERNS OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY IN THE DOG

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IN THE course of studies on experimental cardiac infarction it became apparent that the choice of a relatively constant site for coronary ligation was difficult. To the best of our knowledge there is no anatomic description of the pattern of the artery frequently chosen for ligation, the anterior descending branch of the left coronary artery. Numerous ligation studies have been made on the coronary arteries of dogs, but these have been placed at a distance from the origin of the artery expressed in millimeters rather than having been related to a branching pattern. A measured point is frequently not the corresponding site, in reference to major vessel branching in the area, from animal to animal. In an effort to determine whether or not there was a standard pattern of branching for the anterior descending branch of the left coronary artery in the dog, this anatomy was mapped in fifty dog hearts.

METHODS

The hearts of unselected mongrel dogs coming to sacrifice were collected periodically and stored in saline in the refrigerator for a maximum of two days. Upon the initiation of injection studies, the hearts were then slowly warmed and the anterior descending branch of the left coronary artery was injected with a lead agar mass according to the techniques of Schlesinger.[1] This procedure involves injection under pressure of a colored, warm lead agar suspension into the arteries. Subsequent hardening of the agar results in a cast of a lumen of the arteries. Upon completion of the injection the portions of ventricles containing the anterior descending branch were excised and placed in a 10 per cent formalin solution. The injected arteries were then roentgenographed after placing the injected specimen directly on the film. Tracings were made of the roentgenographic pattern of the artery, and measurements were made of the length and pattern of the various branches.

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RESULTS

In the total of fifty dog hearts studied, a somewhat constant distribution of vessels was noted. A diagrammatic representation of this pattern appears in Fig. 1. Because of the proximity of the septal branch to the coronary ostium, the septal branch was not injected in these studies. However, it has been noted previously[2,5] that the septal branch comes from the anterior descending branch near its origin in about 65 per cent of hearts. In experimental ligation studies, the septal branch was found to supply about 75 per cent of the interventricular septal muscle.[5]

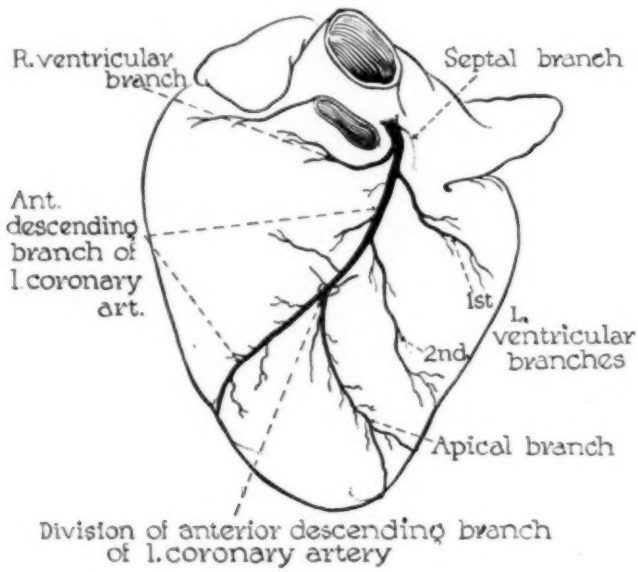

Fig. 1.—Representative pattern of the anterior descending branch of the left coronary artery in the dog.

After giving off the septal branch, the anterior descending coronary artery progresses to the right of the apex in the interventricular groove where its terminal branches anastomose with those of the posterior descending branches of the circumflex artery and/or the right coronary arteries. Along this path there are usually at least two large branches given off to the left ventricle. The first of these, arbitrarily called the first left ventricular branch, supplies a large area of the anterior part of the left ventricular wall. Additional branches of the left ventricle are numbered in sequence from above downward. In three of the hearts studied there was no ventricular branch from the anterior descending coronary artery. Under these circumstances, the blood supply to this portion of the heart was supplied by branches from the circumflex branch of the left coronary artery. In twenty-two of the hearts studied, the left ventricular branch from the anterior descending artery was represented by a single artery; in eighteen there were two left ventricular arteries; in seven there were three ventricular arteries; and in one heart there were four ventricular arteries. When one or more

of these ventricular arteries was present, it was at least one-third as long as the total length of the anterior descending branch in forty-one of the hearts studied. In addition to the ventricular branch or branches, there was an almost constant branch to the apex of the heart. This apical branch had its origin from the upper one-third of the anterior descending branch in twenty hearts, and from the middle one-third of the anterior descending branch in thirty hearts. The apical branch, from the point of its junction with the anterior descending branch, is equal in size (that is, within 5 mm.) to the terminal part of the anterior descending branch in approximately one-half of the hearts. If discrepancies in length of 10 mm. are considered, these two branches are equal in size approximately in three-fourths of the hearts studied.

The branches enumerated above supply portions of the left ventricle. There are also branches to the right ventricle[3] from the anterior descending branch of the left coronary artery. In most instances, these branches are represented by twigs to the right ventricle at irregular intervals along the distribution of the artery. However, in twelve of the hearts studied there was also one large branch, usually arising in the proximal one-third, to the right ventricle. That is, the length of this vessel was equal to at least one-third of the total length of the anterior descending branch in these twelve hearts. The caliber of this vessel, however, seemed to be smaller than vessels of equivalent length supplying the left ventricle. This right ventricular branch was apparently distributed to the upper part of the right ventricle, and occasionally to the adipose tissue around the pulmonary artery. Small vessels, not examined in this study, are described as supplying a small part of the interventricular septum from this area.[5]

DISCUSSION

It is realized that there are certain limitations and errors inherent in the injection study of arterial distribution. The manipulation of pressure and temperature necessary to secure good injections will certainly result in small errors in filling. However, these small errors should not significantly alter the mapping of the major arterial pattern, and it would appear from these studies that there is a relatively constant pattern of the branches of the anterior descending division of the left coronary artery. These are: (1) a septal branch, (2) a left ventricular branch or branches numbered in sequence, (3) an apical branch, and (4) a large branch to the right ventricle in approximately one-fourth of the hearts studied. The portion of the anterior descending branch distal to the origin of the apical branch is called the terminal part. This point of junction is termed the "division of the anterior descending branch" in older literature.[4]

The apical branch and the terminal part of the anterior descending branch are frequently (35 of 50 hearts) comparable in size. Ligation of the coronary artery just above this branching produces a subendocardial infarct (to be reported). Ligation higher than this point is likely to involve one or more of the arteries which have arbitrarily been called left ventricular branches of the anterior descending coronary artery and which have been numbered sequentially. If comparable studies are to be made after coronary ligation in the dog, it is imper-

ative that the anatomy of the artery be carefully considered in order that those hearts which do not conform to a predetermined arterial pattern can be eliminated from the studies.

SUMMARY

The anterior descending branch of the left coronary artery has been injected in fifty dog hearts according to the Schlesinger technique and the anatomic patterns of branching have been outlined.

The authors are grateful to William B. Wartman, M.D., Professor of Pathology, Northwestern University Medical School, for his assistance in this work.

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MASSIVE LEFT ATRIAL THROMBOSIS AND RECURRING PLEURAL EFFUSION

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REPORTS of massive atrial thrombosis have appeared periodically in the medical literature since the early 1800's, and a fairly uniform set of symptoms and physical findings have been elucidated. These reports, in almost all instances, have referred to the "ball valve" action of the thrombus at the mitral valve, and the resulting symptom complex has been the result of intermittent severe limitation of left ventricular output.

Recently we have had the opportunity of observing two cases of massive left atrial thrombosis which have presented a prominent physical finding—recurrent pleural effusion—which has not, to our knowledge, been previously reported. This finding we have attributed to the fact that in each instance the pulmonary venous return from the lung was almost completely obstructed by a thrombus which was attached to the atrial wall.

CASE REPORTS

CASE 1.—L. L., a 61-year-old white woman, was admitted to the Brooklyn Hospital on Jan. 27, 1953, complaining of increasingly frequent anginal attacks and exertional dyspnea. There had been an admission in 1937 for a left lower lobe pneumonia. At that time, a history of influenza in 1918 and pleurisy in 1908 was obtained. Roentgenograms at that time showed a normal cardiac silhouette, and no heart murmurs were heard.

The second admission was in September, 1951, at which time the patient complained of numbness of the right hand and foot of one week's duration, and mental confusion and difficulty with speech of one day's duration. On physical examination, the lungs were clear, no cardiac murmurs were heard, and no abdominal organs or masses were felt. There was a weakness of the entire right side, a supranuclear right facial paralysis and downward drift of the right arm, and all deep tendon reflexes were hyperactive but equal. There was no Babinski reflex. Roentgenograms of the skull demonstrated a destructive lesion in the lateral portion of the petrous pyramid, suggestive of tumor. A skeletal survey failed to reveal any other abnormalities. Roentgenograms of the gastrointestinal tract and retrograde pyelograms were also normal. The chest roentgenograms showed left atrial and left ventricular enlargement. The pelvic examination was within normal limits. The neurologic abnormalities and dysarthria cleared spontaneously, and the patient was discharged in twelve days.

The third admission was in July, 1952, at which time the patient complained of severe retrosternal pain radiating to the left arm. She gave a history of myocardial infarction in October, 1951, for which she was hospitalized in another state. Since then she had been having attacks of retrosternal pain which responded to nitroglycerine. The patient was dyspneic and cyanotic.

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The heart rate was 140, totally irregular, and no murmurs could be made out. The lungs had fine râles throughout, with dullness in both bases and wheezes in the apices. The liver edge was three finger breadths below the right costal margin, and there was bilateral pretibial edema. The patient was digitalized and started on anticoagulants with a provisional diagnosis of myocardial infarction. The following day the heart rate had slowed to 100, and a loud, snapping mitral first sound with a long, rumbling diastolic murmur at the apex was heard. An electrocardiogram

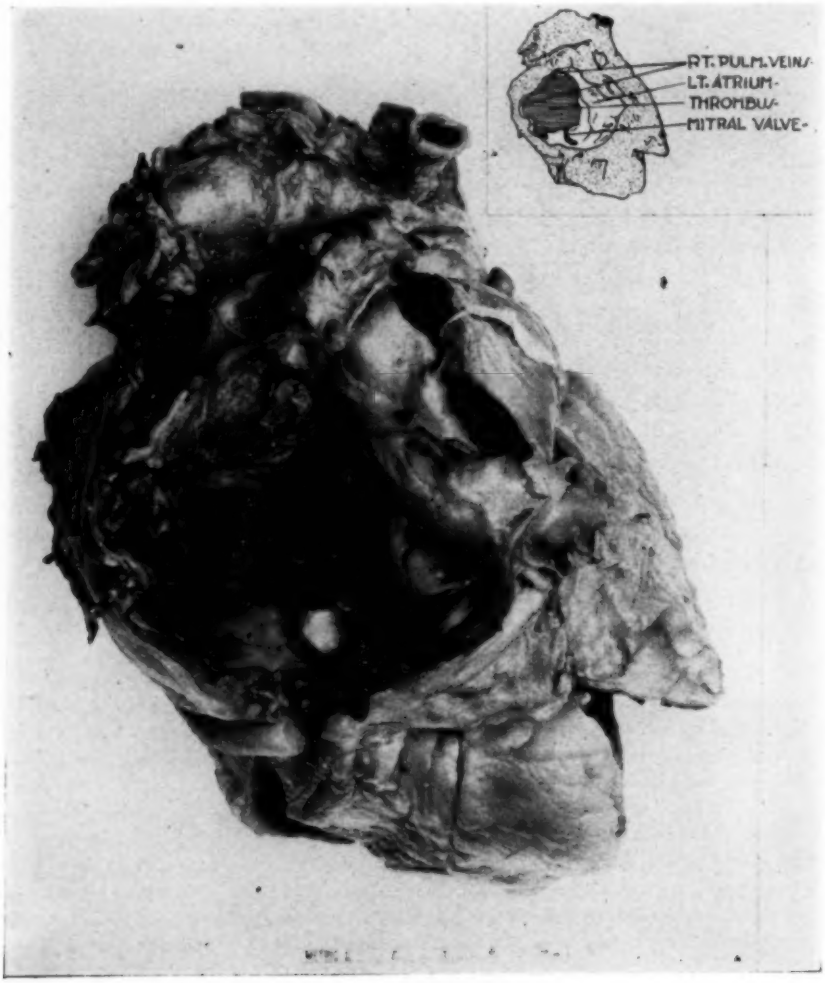

Fig. 1.—Case 1. The left atrium has been opened through the orifices of the right pulmonary veins. The mural thrombus can be seen to protrude into and partially obstruct the veins as they enter the atrium. The left pulmonary veins, which cannot be seen, were also obstructed.

on the third hospital day failed to reveal any changes suggestive of infarction, and since the white blood count and the sedimentation rate were still well within normal limits, anticoagulants were discontinued. The heart failure was controlled with mercurials and digitalis. The patient then developed a persistent fever of 101° to 102° F., which failed to respond to penicillin or Aureomycin therapy. Repeated blood cultures and agglutinations for typhoid fever, typhus fever, and brucellosis were negative. The sedimentation rate and white blood count remained within normal limits. Frequent chest films showed an area of infiltration at the right base which gradually resolved. The fever persisted over a period of six to seven weeks and then disappeared. The patient was discharged feeling better Oct. 1, 1952.

The final admission was three months later. On physical examination, there was cyanosis of the lips and nail beds, pulse rate was 120 and irregular, the mitral first sound was loud, but no murmurs could be made out by four observers. There were a right-sided pleural effusion and some fine râles in the left axilla. The liver was enlarged to the iliac crest, and there was edema of the ankles and back. Thoracentesis was done on the right side eighteen times during the five months of hospitalization, or about once every nine days, with an average withdrawal of 1,000 c.c. The fluid was sterile on all occasions and did not contain any tumor cells. Repeated roentgenographic examinations showed right pleural effusion with clear left lung fields. Toward the end of the patient's illness, however, a rounded mass suggestive of tumor was demonstrated in the right posterior lung field, but the patient's condition precluded any further study.

The mitral diastolic murmur which could not be heard on admission reappeared about Feb. 5, and then was present until death on July 16, 1953.

The important *post-mortem* findings were confined to the heart and lungs. The pericardial cavity contained 100 c.c. of straw-colored fluid. The surfaces were smooth and glistening.

The heart (Fig. 1) weighed 500 grams. The left atrium was notably dilated and contained a large, laminated thrombus which was tightly adherent to the left lateral and anterior aspect of the atrial wall so that the return flow through the left and the right pulmonary veins was partially blocked. The mitral leaflets were thickened and sclerosed and fixed in position so that the orifice was a narrow, curved slit measuring 2 cm. in length, and 0.4 cm. at its greatest width. There was no evidence of an old myocardial infarction.

The right pleural cavity contained about 250 c.c. of straw-colored fluid, and there were numerous long adhesive bands from the collapsed lung to the parietal pleura. There was only a small amount of free fluid in the left pleural cavity which was practically obliterated by dense adhesions.

The right lung weighed 400 grams, and in the apex of the lower lobe was a tan, poorly circumscribed, firm irregular mass, measuring about 2 cm. in diameter. The left lung weighed 375 grams. Both lungs were congested.

The microscopic examination revealed myocardial hypertrophy and some fibrosis, resulting in prominence of the supporting septa. The thrombus was laminated, only superficially organized, but adherent to the thickened left atrial endocardium. Both lungs contained numerous "heart failure cells," the right lung being extensively atelectatic. There was considerable interstitial fibrosis, and the branches of the pulmonary artery were moderately sclerotic. At least one large artery contained an old, organized thrombus. The "tumor" in the right lower lobe was an old, healed infarct consisting of an area of necrosis surrounded by vascularity and fibrosis; nearby there was a squamous metaplasia of bronchiolar epithelium.

Incidental findings included an inactive paratracheal tuberculoma, a pedunculated adenoma of the duodenum, and another in the sigmoid colon. There was no evidence of any malignant tumor, primary or metastatic.

CASE 2.—M. P., a 38-year-old white salesman, was first admitted in September, 1951, complaining of cough, dyspnea, orthopnea, and low-grade fever. Past history revealed no definite attack of rheumatic fever, but the patient was told he had a heart murmur at age 6. He was asymptomatic until he was 38, at which time he complained of a gnawing epigastric pain and palpitations. A gastrointestinal series at that time revealed a duodenal ulcer, and an electrocardiogram showed auricular fibrillation.

The first hospital admission was in that same year, when he developed congestive heart failure. Roentgenogram at this time revealed a right pleural effusion but failed to demonstrate any definite cardiac enlargement. He was treated with low-sodium diet, mercurials and digitalis, and was discharged with a diagnosis of rheumatic heart disease with mitral stenosis.

The second admission was one month later (November, 1951), at which time the patient gave a seven-day history of recurrent hemoptysis and left-sided chest pain on deep inspiration. Roentgenogram revealed bilateral pleural effusions with a hazy density at the left base, which was thought to represent an area of pneumonitis or infarction. He was treated with anticoagulants and dehydration therapy and discharged improved two weeks later.

The third hospital admission in February, 1952, was to another hospital for evaluation for mitral commissurotomy. Because of a low-grade fever, enlarged spleen, elevated sedimentation rate, anemia, and a report of an unclassifiable streptococcus in one blood culture, a diagnosis of

subacute bacterial endocarditis was made. He was treated with several courses of antibiotic therapy, including penicillin, 5,000,000 units every six hours; streptomycin, 1 Gm. twice a day for twenty-seven days; Aureomycin, 0.5 Gm. four times a day for ten days. He was also given a course of salicylates. Despite these medications, he continued to have a low-grade fever and had occasional bouts of blood-streaked sputum and pleuritic chest pain with no localizing signs. A diagnosis of recurrent pulmonary emboli was made, and he was given anticoagulant therapy. A right-sided thoracentesis was done once every two weeks for relief of dyspnea. On his discharge in July, 1952, after five months of hospitalization, the low-grade fever was still present.

His next admission was in October, 1952. The patient had been treated at home with bed rest, mercurials, digitalis, and was relatively comfortable until the day before admission. At that time, he developed a cough, hemoptysis, and a dull pain in the right anterior chest which was accentuated by coughing but not by breathing. The heart beat was totally irregular, the rate was 140, and murmurs could not be distinguished. There was a pleural effusion at the right base, with fine, crepitant râles at the left base. The liver was enlarged and tender, but the spleen could not be felt. There was no peripheral edema. Roentgenogram at that time showed a right lower and possibly a right middle lobar consolidation associated with considerable pleural effusion on the right. The patient was treated with anticoagulants, penicillin, and dehydration therapy with good results. A right thoracentesis was done on two occasions; this yielded 1,500 and 200 c.c. of amber-colored fluid which was sterile on culture and contained no tumor cells. Roentgenograms done at time of discharge (Nov. 21, 1952) in the position of horizontal Trendelenberg and a lateral decubitus, showed considerable clearing of the right pleural effusion; a persistent shadow at the base of the right upper lobe near the junction of the horizontal and oblique fissures was thought to represent a residuum of a pulmonary infarction. Blood urea at that time was 65 mg. per 100 c.c., creatinine, 1.4 mg. per 100 c.c.

The fifth admission on Dec. 1, 1952, ten days following the previous discharge, was because of fever and right-sided pleural effusion. There were signs of effusion at the right base; heart sounds and murmurs were unchanged from the previous admission. The liver was not palpable. There was no peripheral edema. Bronchoscopy examination, which was done because of the persistence of the shadow at the right base and the rapidly recurring right pleural effusion, revealed a thickened, shortened, buckled carina, and a superficial ulceration on the roof of the bronchus intermedius. Vigorous pulsations of the pulmonary artery adjacent to the wall were visible. Biopsy of the bronchial wall showed no evidence of neoplasm. A right thoracentesis was performed on three occasions, 1,250; 1,000; and 850 c.c. of straw-colored fluid being removed which was sterile when cultured. The gastric washings were negative for tuberculosis. The patient was discharged in seventeen days, somewhat improved.

The final admission was Dec. 28, 1952, ten days later. There was fluid in the right pleural cavity. The liver and spleen were not palpable. Thoracentesis of the right pleural cavity on admission was discontinued after 900 c.c. were removed, and another 1,000 c.c. were removed the following day. Eighteen days later on Jan. 16 2,000 c.c. were removed, and 1,200 c.c. on Jan. 31. This tap was discontinued because of pain. During the period of rapid accumulation of fluid in the right pleural cavity, it was noted that the left chest was free of râles. On one occasion, blood cultures revealed a nonhemolytic streptococcus which was sensitive to penicillin. The patient was treated with 20,000,000 units of penicillin every day in divided doses, with no response. Erythromycin was also used without result. The blood urea rose steadily during this hospitalization, and shortly before death on Feb. 28, 1953, the level was 136 mg. per 100 c.c. of blood.

The *post-mortem* findings of particular interest were in the heart and lungs. The pericardial cavity contained 100 c.c. of clear fluid, and the right pleural cavity contained about 2,500 c.c. of clear pink fluid which was partially coagulated so that there were strands and masses of fibrin floating within it.

The right lung was markedly compressed, with a thickened, opaque pleural surface. The left pleural cavity contained only a slight excess of clear yellow fluid, and there were no adhesions.

The heart (Fig. 2) weighed 500 grams. The right atrium was not unusual, and its appendage was free of thrombus. The tricuspid leaflets were thickened, nodular at their margins of approximation, and their commissures were slightly fused. The left atrium was enlarged, firm, and distended. The right lateral wall and posterior surface of the left atrium were covered by a large, laminated, grayish-yellow thrombus measuring up to 2 cm. in thickness, and having several foci

of mineralization. This thrombus impeded the return flow of blood through the right pulmonary veins. The blood returning through these veins had to dissect between the atrial wall and the thrombus in order to enter the left atrium. The orifices of the left pulmonary veins were unobstructed. The mitral leaflets were thickened and partially fused and held in a fixed position, leaving a slitlike opening about 1 cm. in length, and less than 0.2 cm. in width. The valve was diffusely calcified, and at its edges there were large, ulcerated, calcified nodules. The aortic cusps were freely movable, but slightly scarred, and fused for a short distance at their commissures.

The right lung weighed 450 grams, and the left 550 grams. Both had patchy areas of consolidation, and the right lung was compressed and on sectioning appeared poorly aerated.

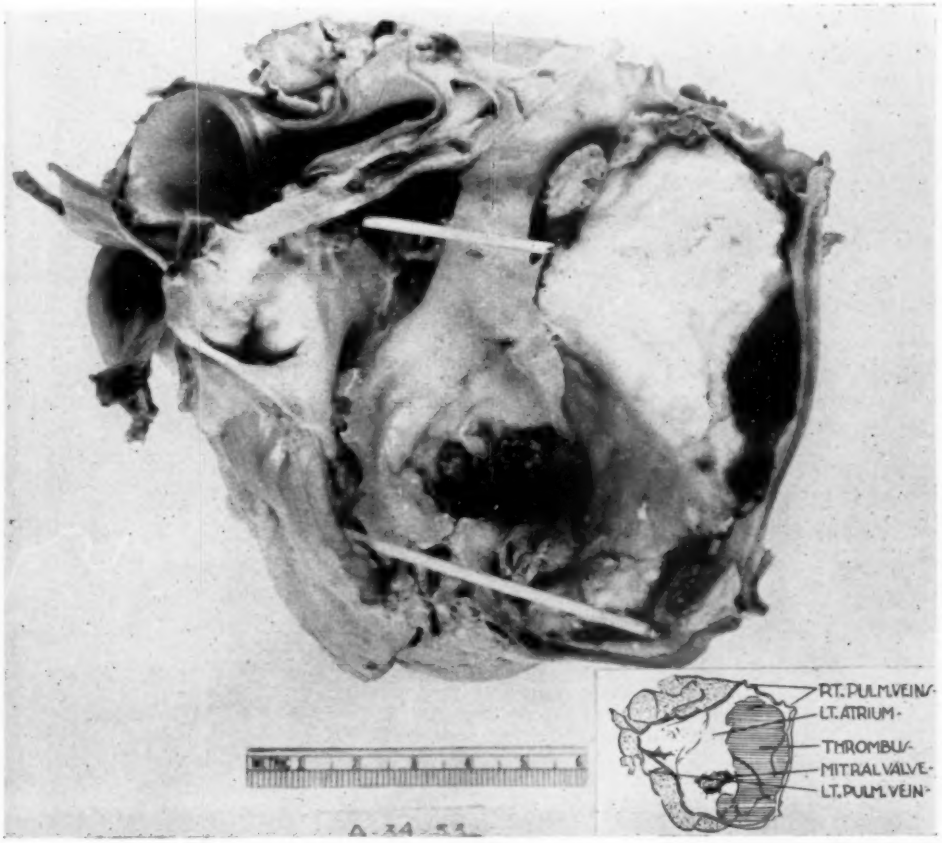

Fig. 2.—Case 2. The left atrium has been cut at the level of the pulmonary veins. The large mural thrombus is transected so that its interference with the emptying of the right pulmonary veins uto the atrium is illustrated. The left pulmonary veins are not obstructed.

The microscopic examination revealed hypertrophy of the myocardium and patchy areas of myocardial degeneration. There was no active rheumatic disease. The atrial thrombus was formed of old, compressed fibrin with only peripheral organization.

In both lungs there were multiple small infarcts. The vasculature was sclerotic, with many vessels having pin-point lumina. Even the small arterioles had thick walls. The infarctions seemed to be on the basis of sclerotic vascular stenosis rather than thrombosis or embolism. Both lungs showed marked passive congestion, with interstitial fibrosis.

There was moderate nephrosclerosis and low-grade pyelonephritis, with occasional tiny parenchymal abscesses. However, there was no focal embolic nephritis and no renal infarcts.

DISCUSSION

These cases are being presented as examples of mechanical interference with the pulmonary venous flow by massive atrial thrombosis which did not directly involve the veins themselves. They also demonstrate the presence of rapidly reaccumulating pleural effusion. This finding would seem to be of considerable diagnostic significance since it is not recorded in previous reports of massive atrial thrombosis. The literature concerning massive atrial thrombosis usually refers to the ball valve type of thrombus which is attached by a small pedicle to one wall of the atria, or to the auricular appendage, and which either intermittently or continuously partially occludes the mitral valve orifice. The resulting symptoms are typical of greatly diminished left ventricular output.

There have been isolated reports which mentioned thrombus either partially or totally occluding the pulmonary veins, but there has been no mention of pleural effusion in these cases.

While the mural thrombus in the first case obstructed the return flow from both lungs, there was little left-sided effusion because the left pleural space was largely obliterated by old fibrous adhesions. The second case had obstruction of the right pulmonary return flow only, and associated recurrent right-sided effusion. While both patients had pulmonary emboli which might account for pleural effusions, it is felt that the rapid refilling was distinctly out of proportion to the embolic phenomena, and that the unilateral involvement was in relation to the pulmonary venosis obstruction.

From these observations, it is suggested that a patient with rheumatic heart disease who has mitral stenosis and auricular fibrillation and who rapidly accumulates fluid in one or both pleural cavities should be suspected of having massive left atrial thrombosis.* With the rapidly developing advances in cardiac surgery, this physical finding may be of importance in the proper evaluation of cardiac patients for mitral commissurotomy.

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*The relationship between recurrent hydrothorax and obstruction of the pulmonary veins by the mural thrombus is suggested but not proved by these cases. There are instances of recurrent pleural effusions with mitral stenosis, atrial fibrillation and pulmonary infarction where the pulmonary veins are not obstructed. Editor.

Clinical Reports

A CONGENITAL SUBCLAVIAN ARTERIOVENOUS FISTULA AND A TRUNCUS BRACHIOCEPHALICUS TOTALIS IN THE SAME PATIENT

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MICROSCOPIC arteriovenous communications are normal phenomena in the regulatory mechanism of the blood circulation. In studying conditions in fetal life, Sabin[1] found the direction of flow in certain blood vessels wholly reversed. Thus, for instance, communications have been encountered in the fetus between the subclavian artery and vein.[2] However, congenital arteriovenous fistulas proper appear to be comparatively rare. Among the 447 cases of arteriovenous fistula collected from the literature, Callander[3] found only three that definitely were congenital in origin. Pemberton and Saint[4] reported nine cases in the material of the Mayo Clinic in 1916 to 1928. Adams[5] collected twenty-two cases of congenital arteriovenous and cirsoid aneurysms. In the literature at our disposal we have found only two cases in which the fistula was in the area of distribution of the subclavian artery. The first of these cases, in which the communication was situated between the right subclavian and transversalis colli vessels, was reported by Reid[6] in 1925. Pemberton and Saint[4] described a very interesting case in which multiple arteriovenous fistulas were present in the upper right extremity. The radial and ulnar arteries were ligated but in the following year amputation of the arm was necessary because of gangrene. Four years later the patient complained of a pronounced thrill in the stump, which was most evident in the region of the clavicle. An increased oxygen saturation of the venous blood confirmed the diagnosis of an arteriovenous fistula, apparently situated between the subclavian vessels. However, no further surgical measures were taken.

The following report covers a case of congenital subclavian arteriovenous fistula which was successfully treated by surgical operation. A further anomaly in this patient was the exceedingly rare truncus brachiocephalicus totalis, on the occurrence of which no reports have been found in the literature at our disposal.

CASE REPORT

A farmer's wife, aged 34 years, had been in rather poor health since childhood. When 8 years of age, she was told that she had "congenital heart disease," which was manifested by a

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loud bruit in the lower part of the neck on the right side. On exertion there had been a stitch and pain in the chest, and more recently there had been twitching and pain in the extremities. The patient had had four normal deliveries and two abortions. She had been admitted to the hospital of the Wihuri Research Institute for observation and was transferred to the First University Surgical Clinic for operative treatment.

On admission the patient was in a good physical condition. Mentally she was rather labile but no unusual neurologic findings were found. The extremities were symmetrical, and there was no hypertrophy. In the right upper arm and on the right side of the neck a continuous bruit was both palpable and audible. It was accentuated with the systole and was maximal over the right supraclavicular fossa. In the upper thoracic region this adventitious sound completely masked the heart sounds. The blood pressure in both arms was 120/75 mm. Hg. The roentgenogram showed a somewhat prominent pulmonary arch and a fairly large-sized heart. The lung findings were normal. Blood tests showed no deviations from the normal and gave the following values: hemoglobin (Sahli), 86; erythrocytes, 4.80 million; color index, 0.90; leukocytes, 5,000; segmented neutrophils, 63.5 per cent; monocytes, 8.5 per cent; lymphocytes, 28.0 per cent; sedimentation rate, 4 mm.

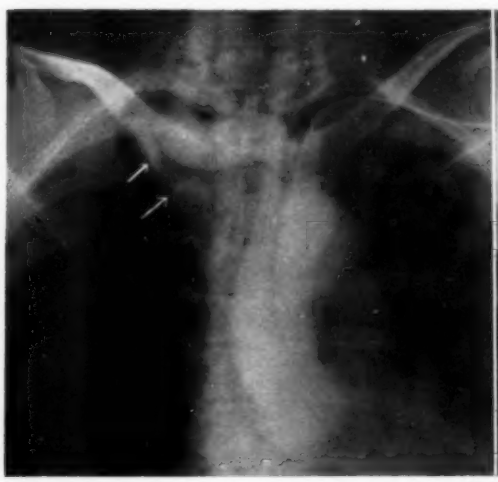

Fig. 1.

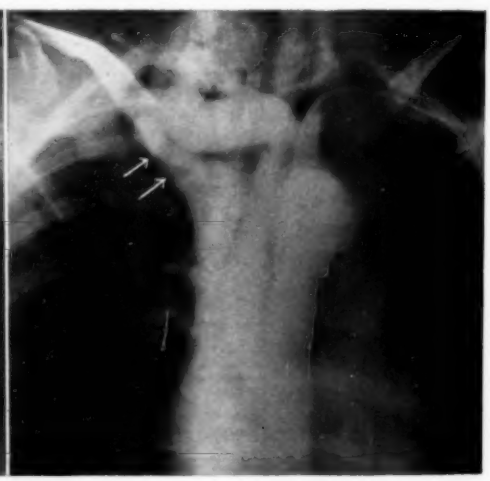

Fig. 2.

Fig. 1.—Thoracic aortogram in the reported case, photographed immediately after the injection of contrast medium. It shows clearly the anomalous truncus brachiocephalicus dextra, arising from the truncus brachiocephalicus totalis on the left and proceeding horizontally to the right. A very small amount of contrast medium has passed into the subclavian vein (marked with arrows). The contrast medium catheter is seen in the left subclavian artery.

Fig. 2.—Aortogram taken 2 seconds later. The contrast medium has passed through the congenital fistula into the subclavian vein, which is now filled with medium (arrows). Note that the subclavian artery is not visible distal to the fistula.

In the aortogram the branches of the aortic arch were seen to arise from the left side, apparently as a single large vessel, a kind of truncus brachiocephalicus totalis.* The right brachiocephalic trunk, 22 mm. in diameter, passed in a horizontal direction from this large trunk to the right side of the chest, on a level with the superior margin of the sternum (Figs. 1 and 2). Almost immediately after the bifurcation of the right common carotid artery, the contrast medium passed through an obvious shunt into the subclavian vein and thence to the vena cava superior (Fig. 2). The fistula was observed to be behind the right clavicle, at the junction of the median and the middle third of the clavicle. A further finding was a small patent ductus arteriosus Botalli (Fig. 3).

A surgical operation was performed on Jan. 8, 1953 (O. Peräsalo). The operation field was exposed by sternoclavicular mediastinotomy according to the method of Killian. A skin incision was made from the inferior portion of the left sternocleidomastoid across the upper sternum to

*Previously called in the literature *arteria anonyma* (innominate artery).

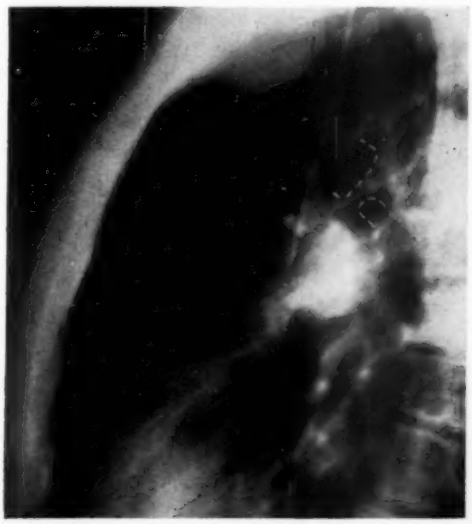

Fig. 3.—Lateral aortogram, showing a minute patent ductus arteriosus (dotted line).

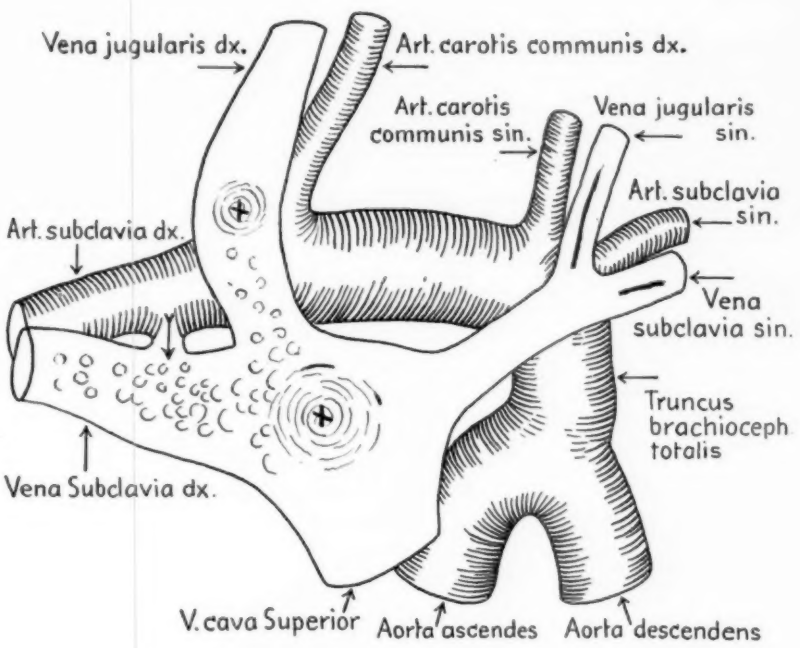

Fig. 4.—Diagram showing relationship between the arteries and veins, as seen at operation. The aorta gives rise to a single branch, a truncus brachiocephalicus totalis, from which then arise, among other blood vessels, the left subclavian artery and the left common carotid artery. The fistula between the subclavian artery and vein (arrow) has a relatively peripheral localization. Strong eddies of blood (x) were seen in the right subclavian and jugular veins, which were greatly distended at these places. The third congenital vascular anomaly in this patient, an open ductus arteriosus, is not shown in the diagram.

the right infraclavicular fossa. The surgeon's finger was introduced through the jugular fossa to the dorsal aspect of the manubrium. A hole was drilled in the center of the manubrium, guided by palpation of the dorsal surface. Starting from this hole, the superior portion of the manubrium was split in the median line with a Gigli saw, and the cut was carried through from the hole to between the clavicle and the first rib. When the muscles attached to the inferior surface of the clavicle were severed, the clavicle with the attached portion of manubrium could be reflected upward and sideways without injury to the pleura. In the enormously distended brachiocephalic vein which was then exposed, a powerful bruit was felt and a strong eddying of lighter and darker blood was visible through its wall. The right jugular vein was also greatly dilated, and when it was divided the underlying brachiocephalic trunk, which was thicker than a man's thumb and passed horizontally from the left, was exposed. There was a bruit in all the blood vessels. An arteriovenous anastomotic blood vessel about the size of a pencil was seen between the subclavian artery and vein (Fig. 4). When this vessel was closed by compression and ligated with three linen sutures the powerful bruit in the blood vessels ceased. The piece detached from the manubrium was replaced and fixed with steel wire and the soft parts of the wound were sutured anatomically. Following the operation there was no change in the blood pressure or the pulse rate, and the patient was dismissed as convalescent on the fourteenth postoperative day.

COMMENT

In this case a congenital arteriovenous fistula between the subclavian artery and the corresponding vein was found at operation. Aortography performed preoperatively seemed to suggest a fistula between the subclavian artery and the brachiocephalic vein. Another congenital shunt, a small patent ductus arteriosus, was also present, but both the subjective and the objective symptoms from this anomaly were relatively mild. A further finding was a single branch of the aortic arch, consisting of a kind of truncus brachiocephalicus totalis. According to Pesonen,[7] this anomaly is chiefly encountered only as a variation in certain animals.

The untoward subjective symptoms from the subclavian arteriovenous fistula were a bruit on the side of the neck and a stitch in the region of the heart, radiating to the right side of the neck after even minor exertion. There was also lassitude.

The attention of the surgeon has been drawn to the pathophysiology and treatment of arteriovenous fistulas chiefly by the traumatic abnormality resulting from war wounds. For a long time following the failure to repair arteriovenous aneurysms by ligation of the proximal vessels, treatment was conservative only, and the fistulas were not considered to be of any great significance. Active treatment was not introduced generally until in the 1920's, after the harmful effect of the fistula on the entire blood circulation had been recognized. Concerning traumatic and similar aneurysms, reference is made to the cases reported by Matas,[8] Aalto[9] and Lievonen.[10]

It is the usual course in cases of arteriovenous fistula that a communication of no deleterious effect gradually becomes enlarged[6] and at the same time, as the pressure decreases, the afferent artery becomes distended, and degenerative changes take place in the arterial wall.[11] In addition to the venefication of the artery, there is also dilatation of the vein and thickening of its wall. There also develops a very abundant collateral network, with its origin on the distal side of the fistula. Both the shunt in the blood circulation and the large volume of blood bound by the slow and abundant collateral circulation and by the increased capillary network lead to an increased minute volume output and a greater

cardiac output as well as to enlargement of the heart, the last mentioned being directly comparable to the size of the shunt.[11]

In the growing period there may be considerable hypertrophy of the heart muscle, and thus even a greatly hypertrophied heart in association with an arteriovenous fistula which is congenital in origin or acquired in the growing period may be found to be fully compensated. In our case, for instance, there were no symptoms of cardiac insufficiency. Holman[11] has described two cases of arteriovenous fistula in which a severe, slowly developed cardiac insufficiency (edema, ascites, hydrothorax) disappeared after closure of the fistula. He also observed in experimental studies that the heart is reduced in size during the first 24 to 48 hours after the formation of a fistula but that hypertrophy already starts by the fourth or fifth day.

In association with arteriovenous fistulas, especially those of congenital origin, there is frequently hypertrophy of the affected extremity. This finding in combination with a continuous bruit is almost pathognomonic of arteriovenous fistulas. In the case described, in which the fistula was situated fairly medially, the extremity was not hypertrophied. An immediate fall in the pulse rate and elevation of the blood pressure on compression of the site of the fistula are regarded as dependable signs for the diagnosis and localization of an arteriovenous fistula. This was not seen in our patient at operation, and in view of the situation of the fistula the test could not be made preoperatively. Since congenital arteriovenous fistulas very frequently are multiple, arteriography is preferable before surgical repair is undertaken.

TREATMENT

For successful therapeutic results, complete closure of the shunt is necessary. If the only measure undertaken is ligation of the proximal blood vessels, the collateral circulation will continue through the shunt, resulting in aggravation of the peripheral conditions. The latter treatment has lately been restricted chiefly to certain intracranial arteriovenous fistulas, and particularly to cases of exophthalmus pulsans. Of the more common methods of treatment, the following are those which are most frequently indicated: (1) ligation of the fistula and its possible division, (2) excision of the entire fistular communication, (3) quadruple ligation, consisting of proximal and distal ligation of the artery and the vein, and (4) transvenous suture of the fistula. Holman[12] found by measurement of the changes in the peripheral arterial pressure that the optimal location of the arterial ligature is, superior to the fistula, directly distal to the main collateral branch and, inferior to the fistula, proximal to the large collateral branch.

For access to the brachiocephalic blood vessel area, Holman,[12] among others, suggests subperiostal resection of the median portion of the clavicle. He reported good movement of the extremity after three weeks. The sternoclavicular mediastonotomy described by Killian[13] and used in our case gives very good exposure of the operation field. It can be conveniently extended bilaterally, and the clavicle and the important sternoclavicular articulation remain intact. Technically, it is less difficult than a carefully performed subperiostal resection of the clavicle. If necessary, it also gives ready access more caudally when the sternum is bisected and the sternocostal part reflected laterally.[14,15]

As arteriovenous fistulas have a progressive tendency, surgical repair is always indicated. In the case of traumatic fistulas it appears desirable to postpone the operation until the time that collateral circulation is established a few months after the occurrence of the trauma, unless an immediate danger of gangrene calls for undelayed treatment. During this period, spontaneous recovery may take place in a few cases, according to Shumacker[16] in about 2 per cent of all cases. Reid[6] stated that an arteriovenous fistula is an even more effective stimulus to collateral circulation than an arterial ligature, and he suggested waiting 3 to 6 months from the occurrence of the trauma. This, of course, is unnecessary in cases in which the lumen of the blood vessels and especially of the artery can be maintained intact.

SUMMARY

A congenital arteriovenous fistula between the subclavian artery and vein is rare. In the reported case of a 34-year-old woman a fistula was found in this situation at operation. Thoracic aortography revealed also a very small patent ductus arteriosus and a single branch of the aortic arch, consisting of a rarely encountered truncus brachiocephalicus totalis. The latter observation was also confirmed at operation. The arteriovenous fistula in the subclavian blood vessels was successfully obliterated by ligation.

The symptoms and pathophysiology of arteriovenous aneurysms as well as their treatment are also discussed. The complete closure of the fistula is indispensable if treatment is to be successful. This is necessary especially for the reason that arteriovenous fistulas have a tendency to progress, which may lead to severe cardiac insufficiency with destructive consequences.

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MITRAL COMMISSUROTOMY FOLLOWED BY LATE ARTERIAL EMBOLISM

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SINCE the inception of mitral valve surgery and the widespread application of commissurotomy, numerous reports have attested to its beneficial results in properly selected patients with mitral stenosis.[1,2] While peripheral emboli have been encountered during and immediately (twenty-four to forty-eight hours) following surgery,[3] all writers, until recently,[4] have stressed the rarity of late embolic episodes following left auricular appendectomy and mitral commissurotomy. As a result, the occurrence of embolic manifestations has been accepted as an indication for such surgery.

For this reason, the appearance of late postoperative peripheral embolization should receive more attention. The detailed description in a number of patients may thereby permit clearer understanding of the pertinent factors responsible in each case, and consequently better selection of patients for surgery.

The following is a report of a patient who suffered a right femoral arterial and aortic saddle embolism two months after mitral commissurotomy and left auricular appendectomy.

CASE REPORT

L. H., a married woman 53 years of age, was first seen by one of us (J. G.) on Dec. 26, 1952, six days after she had suddenly lost consciousness for several minutes, and, upon recovering, noticed left-sided paresis, awkwardness in the use of her left hand, and drooping of the left angle of her mouth. During the following four days, her motor functions had recovered almost completely.. Except for slight exertional dyspnea, she had had no other recent symptoms.

The patient recalled no symptoms of previous rheumatic disease. Neither joint pains nor other manifestations had ever been present. In 1939, she had pneumonia, but was otherwise well throughout her adult life until three years before when she suffered a "heart attack" manifested by substernal tightness, dyspnea, and transient heaviness in the left shoulder. At that time, her cardiac rhythm was grossly irregular, the impression of auricular fibrillation being confirmed by electrocardiography; the ventricular rate was between 160 and 170 per minute. Quinidine was unsuccessful in converting her rhythm, but following digitalization, the ventricular rate fell progressively, although the irregularity persisted. At that time, the patient was said to have developed thrombophlebitis of both lower extremities and was treated with Dicumarol.

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Thereafter, she remained in auricular fibrillation. However, except for some occasional nausea, probably related to digitoxin, and minimal dyspnea, she remained asymptomatic. In January, 1952, she experienced sudden "dizziness" without loss of consciousness, incoherent speech, and tingling of the fingers of both hands, lasting ten to fifteen minutes, and followed by fatigue but no other sequelae.

On physical examination, the patient did not appear acutely ill, the only residua consisting of very slight asymmetry of the mouth, questionable deviation of the extended tongue toward the left, and minimal impairment of fine movements of the left hand. Sensation was entirely intact. The deep tendon reflexes were hyperactive throughout, but no inequality between the two sides or pathologic reflexes were observed. The chest was clear throughout. Cardiac examination revealed the presence of auricular fibrillation with a ventricular rate of about 96 per minute. Clinically the heart did not appear to be enlarged. On auscultation, a loud, sharp, apical first sound and classical crescendo mitral diastolic murmur of mitral stenosis were heard. The second sound was louder over the pulmonic than over the aortic area. The blood pressure was 136/82 mm. Hg. Neither hepatic enlargement nor edema was evident. Peripheral vessels exhibited normal pulsations.

Routine examination of peripheral blood, fasting blood glucose, urea nitrogen, and urine revealed no abnormalities. The roentgenogram of the chest demonstrated clear lung fields with some blunting of the costophrenic sulcus by pleural thickening. In the postero-anterior view, the heart presented a triangular configuration typical of mitral stenosis. On cardiac fluoroscopy, the left ventricle appeared to be normal in size, the right ventricle was minimally, and the left atrium, moderately enlarged. The right pulmonary segment was slightly dilated. Calcification was visible at the site of the mitral valve. Circulation time was seventeen seconds with Decholin, nine seconds with ether. Venous pressure was eleven centimeters of water. The electrocardiogram revealed nothing abnormal other than the arrhythmia.

Despite the absence of any significant cardiac symptoms, it was felt that the history of at least two occurrences of cerebral emboli constituted sufficient indication for left auricular appendectomy and mitral commissurotomy. It was hoped, by removing the auricular appendage, to prevent future dislodgment of thrombotic material. Since clinical evidence of constriction of the mitral valve orifice was present, it was decided to perform a commissurotomy at the same time.

Accordingly, on Jan. 15, 1953, the combined operative procedure was performed by one of us (A. K.). The surgery was well tolerated, and the patient's postoperative course was entirely uneventful. She was discharged on the twelfth postoperative day. At this time she was asymptomatic, although with auricular fibrillation and normal ventricular rate. Maintenance dosage of digitalis was continued.

The patient remained well and was moderately active until March 11, 1953, when she was suddenly seized by a severe pain and sensation of heaviness in the anterolateral aspect of the right thigh, followed by coldness and numbness of the toes and feet of that side. When examined in the hospital thirty minutes later, both feet felt cool, the right more so. A dusky discoloration of the toes of the right foot was present. The toes could be moved only slightly and with difficulty. Hypalgesia extended upward to the level of the mid-thigh. Both femoral arteries were readily palpable just below the inguinal ligament, the pulsations being approximately equal, but neither the popliteal nor dorsalis pedis artery could be felt on the right. Auricular fibrillation was present. Priscoline was injected into the femoral artery without producing any striking effects.

Shortly afterward, while the patient was being prepared for surgery for the removal of a right femoral arterial embolus, the pulsations in both femoral arteries disappeared simultaneously. The skin of the right lower extremity became cold, with mottled cyanosis, and the patient became entirely unable to move her right toes and foot. The left lower extremity was cooler than previously, and difficulty was experienced in moving the left toes. No significant pain was present. A diagnosis of saddle embolus of the aorta was made.

Two separate operative procedures were performed. Under spinal anesthesia, the aorta was approached transabdominally. An embolus was removed from the bifurcation of the aorta through a 1.5 cm. incision in the right common iliac artery. The arterial incision was closed with a continuous 00000 silk everting mattress suture. Upon release of the clamps, pulsations returned promptly throughout the left lower extremity. However, no pulsations were palpable

on the right side below the femoral artery. Therefore, after closing the abdomen, a second incision was made over the right femoral artery, and an embolus removed from the region of the origin of the profunda branch.

Almost immediately following the removal of the embolus, there was rapid return of pulsations and normal color and function in the right lower extremity. The patient's postoperative course was without incident. Twenty-four hours postoperatively, the patient was started on anticoagulant therapy, and was maintained on Dicumarol for four months. Prior to discharge from the hospital, quinidine sulfate was administered in an attempt to convert her auricular fibrillation to regular sinus rhythm, with only partial success. She has been entirely well since.

DISCUSSION

The rarity of late peripheral embolism after mitral commissurotomy appears to be well established. Reports from those centers where large numbers of patients have been treated are in agreement in this respect.[5,6] In general, the large distances between the hospitals and the homes of many patients tend to reduce the number of complete follow-up studies. It is unlikely, however, that any significant number of emboli of any size would fail to reach the attention of the surgeon. It is difficult to understand this observation. As a rule, the operative procedure has little permanent influence on the patient's cardiac rhythm. While the left auricular appendage may be the site of most thrombi in auricular fibrillation, they are by no means absent in the atrium proper, and as such, are capable of producing emboli. Although the auricle is flushed out and presumably freed of clots during surgical exposure of the valve, some of the conditions leading to thrombus formation in the fibrillating atrium are unchanged postoperatively. However, the absence of a noncontractile sac, the reduced pressures and volume of the chamber, and increased flow of blood all would tend to diminish the likelihood of intra-atrial thrombi.

Should the experience here reported be encountered with greater frequency, perhaps other possible sites should be considered. Firstly, until regrowth of the endocardium over this area is complete, the line of closure of the amputated auricular appendage may conceivably be a site for the origin of thrombi. It was partly with this possibility in mind that the patient was placed on anticoagulant therapy. Secondly, in some patients, the existence of rheumatic activity and rheumatic endocarditis associated with mural thrombi may predispose to emboli. However, no evidence of rheumatic activity was present in this patient. Thirdly, the traumatized endocardial surface of the ruptured valve leaflet(s) may provide a fertile surface for thrombus formation. However, the very agitated movements of the valve and surrounding turbulence would appear to render this a rather remote possibility.

The decision to employ anticoagulants was based upon several considerations. In the absence of previous experience, one could not predict with any degree of certainity whether the probability of future emboli in our patient was equal to or greater than in other postcommissurotomy patients. In short, was this embolus a random event, or did it signify a greater degree of susceptibility? A conservative approach was employed. In order to reduce the probability of clotting and emboli both in the heart and in the peripheral vessels, the patient was maintained on Dicumarol much longer than necessary to permit complete endothelial covering of the tissues underlying the point of attachment of the thrombus.

By the same token, in order to reduce further the probability of recurrences should these prove to be more frequent than previously suspected, perhaps more vigorous attempts to convert auricular fibrillation to regular sinus rhythm should be undertaken. As a rule, in chronic auricular fibrillation, such endeavors will not be successful, but when regular rhythm can be restored and maintained without undue difficulty, the likelihood of thrombus formation should be further reduced.

SUMMARY

The case report of a patient who experienced peripheral emboli eight weeks after left auricular appendectomy and mitral commissurotomy is presented. The factors which may contribute to the recurrence of emboli and to the prevention thereof are discussed.

ADDENDUM

Since this report was submitted, three additional instances of late arterial embolism following mitral surgery have occurred.

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DISSOCIATION WITH DOUBLE INTERFERENCE

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INTERFERENCE dissociation is a rare form of atrioventricular nodal rhythm. It occurs when in such a rhythm a unidirectional, retrograde block exists in the atrioventricular junction, which prevents the passage of the stimulus from the atrioventricular node from entering into the atria and discharging the sinoauricular node. In these circumstances the atria remain under the control of the sinoauricular node. As the rate of the sinoauricular node is slower than that of the atrioventricular node part of the sinus impulses are prevented from passing into the ventricles because they reach the atrioventricular junction when it is still refractory (interference). The ventricles therefore remain under the control of the atrioventricular node. Only occasionally an impulse of sinus origin reaches the atrioventricular conduction system after it has recovered and passes into the ventricles, at the same time discharging the nodal pacemaker. Characteristically, therefore, in interference dissociation an otherwise regular sequence of nodal beats is now and then interrupted by a "premature" beat of sinus origin.

In recent years it has become evident that besides this common type of interference dissociation an unusual form also exists. The characteristic feature of this uncommon type is that a regular series of nodal beats is interrupted by a longer interval. The reason for this long pause is that a sinus impulse has penetrated and discharged the nodal pacemaker but is prevented from passing into the ventricles since another part of the atrioventricular junction, below the nodal pacemaker, is still refractory. Obviously in these cases the refractory phase of different parts of the atrioventricular junction is not the same, hence the sinus impulse on its way to the ventricles can be arrested at two locations.

Examples of this unusual form of interference dissociation have been described by Cutts,[1] Langendorf and Katz,[2] and Zuidema.[3] It is one form of what Langendorf[4] has called "concealed conduction." Recently Gentile[5] reviewed the literature about this uncommon form of interference dissociation and proposed the name: "dissociation with double interference" or "dissociation with ladder type of interference." The rarity of this condition is evident as (according to Gentile) since 1932 only nine cases have been reported in the literature. To this number he adds two cases of his own. This ladder type of interference has been observed in patients with coronary thrombosis, syphilitic aortitis with angina pectoris, marked depression of the sinus node from obscure origin, and during treatment with digitalis and (or) quinidine.

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Fig. 1.—Sinus rhythm, rate 39; P-R conduction time 0.14 second.

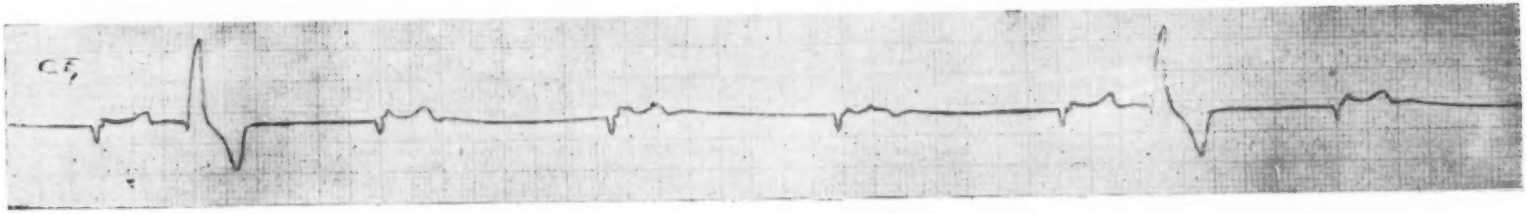

Fig. 2.—Thirty minutes after a subcutaneous injection of 0.5 mg. of atropine sulfate. Interference dissociation. Rate of sinoauricular node 38; rate of atrioventricular node 41.

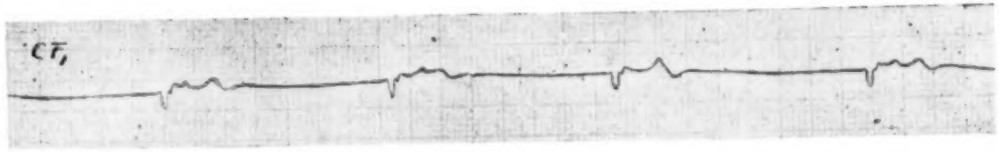

Fig. 3.—Forty-seven minutes after Fig. 2. Dissociation with double interference. See text.

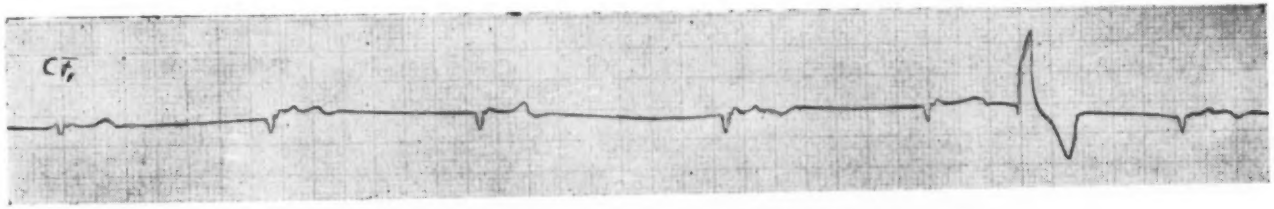

Fig. 4.—Common and uncommon types of interference dissociation in one record.

CASE REPORT

A 28-year-old Chinese man was admitted to the hospital complaining of dizziness. A few weeks before he quite unexpectedly suffered from a fainting spell; afterwards the dizziness remained. Furthermore, the patient noticed some shortness of breath on exertion and was troubled by palpitation. His physician noticed a very slow pulse and suspected complete atrioventricular block with the Adams-Stokes syndrome.

The past history was irrelevant. The patient had not suffered from any infectious disease; he abstained from tobacco and took no medicine.

The patient apparently was in good health but rather nervous. At first examination his pulse rate was 36, sometimes the pulse was not quite regular. The heart was not enlarged; the heart sounds of normal quality; blood pressure, systolic 130, diastolic 70 mm. Hg. In the neck no lymph glands could be felt. The eyegrounds were normal. The urine contained no albumen and no sugar. Urea concentration of the blood was 36 mg. per cent. The Wassermann and Kahn tests in the blood were negative. Roentgenographic examination of the thorax showed a normal heart shadow and clear lung fields; the barium-filled esophagus showed no diverticulum.

An electrocardiogram (Fig. 1) shows a sinus rhythm with a rate of approximately 39 per minute. The P-R conduction time is 0.14 second. The P-wave pattern is abnormal as the P is negative in all leads. The slow rhythm and short conduction time with the abnormal P waves suggest a rhythm arising in the tail of the sinus node.

In other records sinus arrhythmia was sometimes present with further slowing of the sinus rate. In these circumstances nodal escape often occurred, not only singly but also in pairs. The rate of the atrioventricular node was 35. The appearance of these nodal escapes often resulted in competition between the sinus- and nodal impulses for control of the ventricles.

During his fortnight stay in the hospital the pulse remained slow. The patient was treated with ephedrine, 25 mg. four times a day; with this medicine the sinus rate could be speeded up to 44. The patient, however, still complained of dizziness, but no syncope occurred.

The following experiments were carried out.

A. *Influence of exercise:* Records taken immediately after the patient had sat up and had lain down twenty times showed a slight acceleration; the rate of the sinus pacemaker increased by 7 per minute.

B. *Influence of epinephrine:* After a subcutaneous injection of 0.5 mg. of epinephrine the sinus rate increased to sixty. Short runs of sinus tachycardia with a rate of 94 to 107 occurred.

C. *Influence of atropine:* The effect of a subcutaneous injection of 0.5 mg. of atropine sulfate was studied several times. Invariably the result was the same: the sinus arrhythmia disappeared but the rate of the sinoauricular node almost remained the same. The nodal pacemaker however speeded up and became therefore slightly faster than the sinoauricular node, always with interference dissociation as a result. This is reproduced in Fig. 2, which was taken 30 minutes after a subcutaneous injection of 0.5 mg. of atropine sulfate. The rate of the sinoauricular node remained 38. The rate of the atrioventricular node, however, increased from 35 to 41. In this record, interference dissociation is clearly present; on two occasions the regular nodal rhythm is interrupted by a conducted sinus beat with a prolonged P-R interval (0.24 second) and aberrant conduction in the ventricles. This mechanism continued to exist for more than one hour.

When interference dissociation was first recorded in this patient, the possibility was considered that the phenomenon of double interference might be recorded. At regular intervals records were taken but it lasted until 67 minutes after the atropine injection had been given before a second zone of interference could be demonstrated. Thereafter, it was repeatedly present. Fig. 3, taken 47 minutes after Fig. 2, shows this interference in a second zone of the atrioventricular junction. The time interval between two P waves is 1.52 seconds, corresponding to a sinus rate of 39. The ventricular beats are all nodal in origin; the first three beats show a regular rhythm with a time interval of 1.46 to 1.47 seconds, corresponding to a rate of 41. After the third beat, however, the time interval is suddenly prolonged to 1.65 seconds. The explanation is obvious. In the first and second beats the sinus impulses reach the atrioventricular node during its refrac-

tory phase, but in the third beat the sinus stimulus comes so much later, that it is able to penetrate and to suppress the atrioventricular node. However, some region below the nodal pacemaker is still in the refractory phase and, again by interference, prevents the sinus impulse from passing through into the ventricles.

Sometimes the common and uncommon type of interference dissociation succeeded each other. This is represented in Fig. 4. In this record the uncommon type occurs after the third nodal beat. A conducted sinus beat is seen after the fifth nodal beat.

The same experience was gained from subsequent experiments with atropine sulfate. A second zone of interference could never be demonstrated in the first three quarters of an hour after the injection had been given but was only manifest after the effect of atropine was declining.

TABLE I

	R-P INTERVAL IN SECOND	INTERFERENCE IN THE A.V. NODE	INTERFERENCE IN A SECOND ZONE OF THE A.V. JUNCTION	CONDUCTED SINUS BEAT P-R INTERVAL	SUM OF R-P + P-R INTERVAL OF CONDUCTED SINUS BEAT
10:50 Sinus rhythm, rate 38, P-R interval 0.14 second					
10:53 Subcutaneous injection of 0.5 mg. of atropine sulfate					
11:23 Rate of S. A. node, 39; A.V. node, 42	0.25 or less	always			
	0.29			0.30	0.59
	0.29			0.31	0.60
	0.30			0.30	0.60
	0.30			0.30	0.60
	0.30			0.30	0.60
	0.30			0.30	0.60
	0.31			0.29	0.60
	0.32			0.27	0.59
	0.32			0.28	0.60
	0.33			0.27	0.60
	0.37			0.23	0.60
11:40 Rate of S.A. node, 39; A.V. node, 41	0.24 or less	always			
	0.25			0.36	0.61
	0.26			0.36	0.62
	0.26			0.35	0.61
	0.26			0.37	0.63
	0.26		x		
	0.26			0.38	0.64
	0.27		x		
	0.27		x		
	0.27			0.37	0.64
	0.27		x		
	0.27		x		
	0.28		x		
	0.28		x		
	0.28		x		
	0.29		x		
	0.29		x		
	0.30		x		
	0.30		x		
	0.30		x		
	0.31			0.33	0.64

TABLE I (CONTINUED)

	R-P INTERVAL IN SECOND	INTERFERENCE IN THE A.V. NODE	INTERFERENCE IN A SECOND ZONE OF THE A.V. JUNCTION	CONDUCTED SINUS BEAT P-R INTERVAL	SUM OF R-P + P-R INTERVAL OF CONDUCTED SINUS BEAT
	0.31		x		
	0.32			0.34	0.66
	0.32			0.32	0.64
	0.34			0.27	0.61
	0.34			0.28	0.62
	0.36			0.26	0.62
	0.36			0.26	0.62
	0.36			0.26	0.62
	0.36			0.26	0.62
	0.36			0.26	0.62
	0.37			0.25	0.62
	0.37			0.25	0.62
	0.39			0.21	0.60
	0.41			0.20	0.61
	0.42			0.19	0.61
11:50	0.24 or less	always			
Rate of S.A. node, 38;	0.25			0.36	0.61
A.V. node, 40	0.26			0.38	0.64
	0.26		x		
	0.27		x		
	0.29		x		
	0.29		x		
	0.29		x		
	0.30		x		
	0.31		x		
	0.32		x		
	0.32		x		
	0.33		x		
	0.33			0.33	0.66
	0.33		x		
	0.35			0.26	0.61
	0.42			0.20	0.62
12:10	0.26		x		
	0.27		x		
	0.27		x		
	0.27		x		
	0.29		x		
	0.29		x		
	0.31		x		
	0.31		x		
	0.32		x		
	0.32		x		
	0.33		x		

At that time the vagus nerve regained its influence. Therefore, the possibility had to be considered that an increased vagus tone, (by lengthening of the refractory period of the part of the atrioventricular junction beneath the atrioventricular node) was the cause of this second zone of interference. To that end the several beats of a long record were studied. In every beat the R-P interval was determined together with the fate of the sinus impulse (interference in the atrioventricular node or interference in a second zone of the atrioventricular junction or conduction to the ventricles). In the protocol (Table I) the several beats are arranged in order of the length of their R-P interval.

CONCLUSION

At 11:23 all sinus impulses with a R-P interval of 0.29 second or higher were conducted to the ventricles. At 11:40, however, all sinus impulses with a R-P interval of 0.28, 0.29, and 0.30 second were arrested in the second zone of interference of the atrioventricular junction. And at 11:50 all sinus impulses with a R-P interval of 0.27 to 0.33 second were arrested at this zone. It appears, therefore, that an increase of the vagus tone did not affect the refractory period of the atrioventricular node but resulted in a lengthening of the refractory period of a zone in the atrioventricular junction beneath the atrioventricular node. This caused a second zone of interference for the sinus impulse on its way to the ventricles.

Some authors have suggested that this second zone may be located in the lower part of the atrioventricular node. It seems unlikely, however, that the refractory period of the upper and lower part of the atrioventricular node would differ so much. It seems more reasonable therefore that this second zone of interference is situated between the atrioventricular node and the division of the common bundle.

At 11:50 and 12:10 interference of a sinus beat in the second zone of the atrioventricular junction still occurred with a R-P interval of 0.33 second. As the duration of the P wave amounted to 0.05 second, the absolute refractory period of the atrioventricular junction lasted 0.38 second. This is decidedly much too long, as it is stated, that this period should not exceed 0.25 second. This long refractory period in this patient is in sharp contrast with the short P-R interval, which was only 0.14 second. Certainly this long refractory period points to a pathologic state of the atrioventricular conduction system too.

It may be remarked that in the conducted sinus beats the sum of the R-P and the P-R interval was always between 0.60 and 0.64 second.

The cause of the abnormal depression of the sinoauricular node could not be detected. After his discharge from the hospital the patient remained under the care of his physician. One-half year afterwards the pulse rate was reported to be about 40.

SUMMARY

In dissociation with double interference a regular nodal rhythm is occasionally interrupted by a longer interval. At that time the sinus impulse has penetrated and discharged the atrioventricular node but is prevented from passing into the ventricles by a second zone of interference in the atrioventricular junction. This rare conduction disturbance was studied in a Chinese man with a marked depression of the sinoauricular node from unknown origin. After a subcutaneous injection of 0.5 mg. of atropine sulfate, the common form of interference dissociation at first occurred. When after about one hour the vagus tone was restored a second zone of interference in the atrioventricular conduction system appeared. It could be determined that increase of vagus tone did not influence the refractory period of the atrioventricular node but lengthened the refractory phase of the atrioventricular junction beneath this node, which was the

cause of the unusual form of interference dissociation. The duration of the refractory period of the atrioventricular junction mounted to 0.38 second, which is decidedly pathologic.

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Book Review

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG, 19. TAGUNG. HAUPTTHEMA: KREISLAUF AND GEHIRN. Dr. Rudolf Thauer, Editor. 324 pages, Darmstadt, 1953, Dr. Dietrich Steinkopff.

The book is a collection of 34 papers with discussions, presented at the 19th meeting (April 9-12, 1953) of the Deutsche Gesellschaft für Kreislaufforschung, with cerebral circulation as the main topic.

Kety and Schmidt's method seems to have been generally accepted for measurement of the cerebral circulation and oxygen uptake. Bodechtel (pages 109-131) reports in his review on the clinical picture of disturbances of cerebral circulation, an impressive material of 800 patients in whom this method was used. The cerebral blood flow is severely reduced in the Adams-Stokes syndrome, during cardiac decompensation (11 cases), and cerebral arteriosclerosis (26 cases). Impairment of cerebral circulation is more common in right than in left ventricular insufficiency. On the other hand, it is significantly increased in cor pulmonale due to the increased arterial CO_2 content, producing increase of intracranial pressure with the concomitant syndrome. However, as soon as cardiac decompensation develops, the cerebral blood flow drops below normal.

The decreased cerebral blood flow is the basis of acute (convulsions, loss of consciousness) or more chronic disturbances of the central nervous system. Forty per cent of cyanotic patients with congenital heart disease, in a material of 650 cases of the University Hospital in Boon (Grosse-Brockhoff) had neurologic symptoms. The drop of blood pressure in myocardial infarct may produce the dominating syndrome of a cerebral accident, and only the routinely taken electrocardiogram (ECG) may reveal a myocardial infarct as the underlying cause.

Schneider (pages 1-25) reviews the experimental basis of brain circulation and oxygenation in its application to clinical problems. Extensive animal work in Germany on the effect of CO_2 and O_2 tension, blood pressure, and other fundamental variables on cerebral circulation has paralleled similar investigations in the United States. Section of the neck sympathetic fibers, block of the ganglion stellatum, and sympathicolytic drugs increase the normal cerebral circulation only slightly, if at all, but may increase a previously decreased cerebral circulation very substantially.

A minimum level of cerebral oxygen uptake necessary for maintenance of function is differentiated from the minimum level necessary for maintenance of the structure. The latter is very much lower and approximately 10 per cent of the normal metabolic rate of the brain. Such low level is accompanied with deep coma, but sufficient to keep the structure intact so that the recovery is complete. If the oxygen supply falls below that critical level, irreparable damage occurs depending on the time and degree of ischemia. The critical time for complete arrest of circulation is about 3 to 4 minutes, but a trickle of blood flow has a tremendous effect on the survival time. In one typical experiment with the isolated head of a cat, increase of the cerebral blood flow from 3.3 to 3.8 c.c. per minute shortened the time from the release of ischemia to the appearance of electroencephalographic (EEG) action potentials from 20 to 4.5 seconds. It is concluded that in the reports of revival after cardiac standstill up to 10 minutes, the arrest of cerebral circulation was not quite complete.

There is a remarkable adaptation of the central nervous system to chronic hypoxia; ambulatory patients with pernicious anemia may have values of cerebral O_2 uptake which would produce deep coma in an acute condition.

Of great interest is the finding of an optimum brain temperature between 28 and 32° C. for recovery from ischemia. The recovery time was increased at higher or lower temperatures and was equally long at 38° and 22°. It seems that nothing is gained by cooling the brain below 32°.

Opitz (pages 26-44) discusses the effect of cerebral ischemia on the metabolic changes in the brain. Frequently, the abolishment of reflexes in cerebral ischemia occurs in two phases, separated by an interval of about 20 seconds. The first phase is due to the exhaustion of aerobic and the second one is due to the exhaustion of anerobic energy (glycolysis). The energetic efficiency of glycolysis, however, is very poor. The extreme vulnerability of the brain to oxygen deprivation, as compared to other organs, is due to the very low level of aerobic as well as anaerobic reserves,

in view of its high metabolic rate. It is of interest that, in contrast to the heart or skeletal muscle, the glycogen in the brain is not utilized in the condition of acute ischemia. The cumulative effect of hypoglycemia and impairment of cerebral circulation is discussed more specifically by Höpker (pages 241-246).

The anatomic and pathologic basis for ischemic damage of the brain is reviewed by Scholz (pages 52-69) and by Meyer (pages 69-83). Of particular interest is the observation of local arterial spasms which might explain, in part, the localization of damage in general cerebral ischemia. Other reasons for localization of damage are the different tolerance of various structural elements to hypoxia and a different distribution of the blood flow to various parts of the brain.

Bernsmeier (pages 88-93) suggests in Kety and Schmidt's method to replace the five pairs of blood samples from an artery and the internal jugular vein by two continuous samples taken at constant speed with a motor-driven syringe over a period of ten minutes. This procedure does not only reduce the analytical work but also simplifies the calculation. The agreement of this modification with Kety and Schmidt's original method in parallel determinations was excellent.

Polzer and Schuhfried (pages 93-96) have developed an ingenious qualitative method for measurement of cerebral circulation. A volume pulse of intracranial blood flow is recorded through resistance changes of an alternating current of 30,000 c.p.s. by means of a Wheatstone bridge. The electrodes are put on the forehead and postmastoid region. The pulse contour is similar to the photoelectric finger plethysmogram. The pulse amplitude is calibrated in units resistance. Large differences in amplitude and contour between normal individuals and patients with cerebral arteriosclerosis are demonstrated, quite similar to differences in the peripheral finger or toe volume pulse curve between normal subjects and patients with peripheral arteriosclerosis.

Electroencaphalographic (EEG) changes in experimental and pathologic hypoxia and ischemia are reviewed by Jung (pages 170-196). The EEG is indispensable for the study of functional effects of circulatory impairment, but it is, of course, a qualitative method. The results show the different tolerance of various parts of the central nervous system to oxygen deficit with the cerebral cortex and thalamus as the most vulnerable structures. It is of interest that the sensitivity to experimental hypoxia may be significantly increased in light colds or infections of the upper respiratory tract.

The EEG was used in a study of cerebral effects of cardiac arrest elicited by carotid pressure in patients with the carotid sinus syndrome (Franke and Hann: pages 205-210). Heine (pages 196-200) reports on simultaneous determination of cerebral circulation by means of Bernsmeier's modification of Kety and Schmidt's method and of the EEG in 113 cardiovascular patients. In all cases with normal EEG (normal subjects or patients with decreased cerebral circulation) there was no correlation between the various items of EEG analysis and cerebral circulation. On the other hand, there was some general correlation between cerebral circulation and abnormal EEG changes, but not in all groups of patients. The correlation was best in patients with cor pulmonale, and poorest in patients with cerebral arteriosclerosis. There was no correlation between blood pressure and EEG.

Krump (pages 200-205) found in 62 per cent of 140 patients with arterial hypertension abnormal electroencephalograms, but the changes were classified in most cases as light (34 per cent) or moderate (20 per cent). However, it was definitely normal only in 18 per cent of the group.

Angiography in normal and abnormal cerebral circulation is reviewed by Riechert (pages 131-141), and Gänshirt (pages 218-224) reports on parallel determinations of cerebral circulation by means of Kety and Schmidt's method and angiograms in thirty-three patients with various cerebral tumors.

Weigelin (pages 233-238) studied in a large material of 626 patients with arterial hypertension the correlations between arterial blood pressure, retinal arterial pressure as measured by means of a newly developed method, and changes of the retinal fundus. The correlation coefficient between the retinal and brachial arterial pressure was very high ($r = 0.9$). The correlation between the degree of abnormal fundus changes (subdivided into four classes) and the retinal arterial pressure ($r = 0.6$) or the brachial arterial pressure ($r = 0.53$) was much lower but still statistically significant. However, advanced fundus changes were usually present when the retinal arterial pressure exceeded the level predicted from the brachial arterial pressure on the basis of the regression equation.

It is not possible to review all papers presented at that meeting, but this arbitrary selection is representative for the general high standard of communications and discussions. E. S.

Announcements

THREE POSTGRADUATE COURSES IN PEDIATRIC CARDIOLOGY are to be offered during October, 1954, by COOK COUNTY GRADUATE SCHOOL OF MEDICINE. They will be presented by Benjamin M. Gasul, M.D., Attending Pediatrician and Director of the Cardiac Division of the Cook County Children's Hospital, and Egbert H. Fell, M.D., Attending Surgeon, Cook County Hospital, and Associates.

The courses will be intensive and practical, and are designed for the pediatrician, internist, general practitioner, and roentgenologist. Examination of patients and the detailed study of case histories will utilize the wealth of clinical material available.

Course I

The Diagnosis and Treatment of Congenital and Rheumatic Heart Disease in Infants and Children, one week, starting Oct. 18, 1954.

Course II

Roentgenology and Electrocardiography in Heart Disease in Infants and Children, three days, starting Oct. 11, 1954.

Course III

Angiocardiography and Catheterization of the Heart and Great Vessels in the Diagnosis of Congenital and Acquired Malformations in the Hearts of Infants and Children, three days, starting Oct. 14, 1954.

For information, address: Registrar
707 South Wood Street,
Chicago 12, Illinois

Five distinguished physicians from other countries will be guest speakers at the TWENTY-FIFTH ANNUAL POSTGRADUATE SYMPOSIUM ON HEART DISEASE to be held Oct. 6, 7, 8, 1954 at Larkin Hall in the Civic Auditorium, San Francisco, California. They are Dr. Olov Viking Björk of Stockholm, Sir Russell C. Brock, distinguished London surgeon, Drs. Pedro Cossio and Manuel Rene Malenow, of Buenos Aires, and Dr. Horace Smirk of New Zealand. Dr. Charles T. Dotter of Portland, Oregon, has also accepted the invitation to participate. Other speakers will be announced later.

Five Northern California Heart Associations will cooperate with the San Francisco Heart Association to present this unusual program. Detailed programs will be in the mail by the middle of August. Registrations may be made through the San Francisco Heart Association, 604 Mission Street, San Francisco 5, California.